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FURTHER STUDIES INTO THE HUMAN SERUM FACTOR WHICH CAUSES NECROSIS OF GUINEA-PIG SKIN

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THE CAPACITY of some human sera to cause necrosis when injected intradermally in guinea pigs has been reported.[7] It has been observed, further, that the sera of patients during the "acute phase response" have such an activity.[4,23] This activity of the serum appears to be another example of substances of varying properties which appear, or whose titers increase, during the acute stages of many diseases. C-reactive protein, a sensitive indicator of the presence of inflammatory activity, is a well studied example of this.[26,29,30,45] The streptococcus bactericidal factor[44] and complement[4,10,11,23,28,41,47] are but a few of the others.

Recently, British authors,[4,28] in a study on the necrotizing activity of the sera of patients with a variety of inflammatory conditions, suggested that this activity was a function of the complement fraction of the serum itself. In an independent study, Kuster[23] came to a similar conclusion, although neither work clearly demonstrated the role of complement nor which component of the complement fraction possessed the necrotic potency. A further study of the role of complement with special attention to its fractions in regard to necrosis appeared necessary. This study, therefore, assumed this problem as one for major consideration.

While the British workers did not study the presence of C-reactive protein in their necrotizing sera, close scrutiny of their work suggested that this abnormal protein[20] might well be present in each of these sera.

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By identifying the presence of C-reactive protein in those sera of this study and, further, employing purified C-reactive protein in various serum combinations, it was felt that this aspect of the study could be so accounted for and was done.

The likelihood that all of these sera in guinea pigs caused the release of histamine locally leading to necrosis was also a consideration. A simple but satisfactory method of proving this appeared to be by the use of an injectable antihistamine and histamine. It was in this fashion that the problem was undertaken for evaluation.

MATERIALS AND METHODS

Albino male guinea pigs weighing 300-400 gms were used. They were carefully prepared for injection by shaving the abdominal wall with an electric shaver.

Freshly drawn bloods were permitted to clot in glass tubes from which the sera were then taken out and placed in acid washed tubes. Injections of 0.15 cc undiluted serum were made with a tuberculin syringe and 26-gauge needles intradermally into the abdominal wall.

A lesion was considered necrotic if, twenty-four hours following the injection, a macroscopic yellowish or bluish area of discoloration was seen at the site of inoculation surrounded by a zone of erythema and induration. The mean diameters of these lesions were measured and recorded in millimeters.

C-reactive protein (CRP) precipitin tests were done on all sera by the capillary tube procedure of Anderson and McCarty.[1] A test was read as positive when a precipitate was formed by the interaction of CRP antiserum (CRPA) and the patient's serum. A known negative serum plus the antiserum, and a tube of the patient's serum alone as controls, had to show no visible precipitation; positive controls were also used.

Purified CRP was prepared by the method of MacLeod.[29,33] Then two guinea pigs each were injected, respectively, with: (a) purified CRP in saline, (b) purified CRP added to normal serum, (c) purified CRP added to necrotizing serum with a negative CRP, and (d) necrotizing serum with a positive CRP adsorbed with CRP antiserum and the results noted.

Complement (C′) titers were measured in a hemolytic system of sensitized sheep red blood cells,[21] using the equation of von Krogh:

$$x = k \left\{ \frac{y}{1-y} \right\} 1/n$$

where, $1/n = 0.2$

y = degree of lysis

x = amount of complement used in ml

k = 1 at 50% lysis

and the method of Kabat and Mayer, the 50 per cent unit of hemolysis ($C'H_{50}$) was determined.[17,36]

Veronal buffer was prepared according to the method of Pillemer[9] and adjusted to pH 7.4. All serum dilutions were made with Veronal.[24,25,37] Serum dilutions of 1:20 and 1:40 were selected to give 20 per cent to 90 per cent lysis; however, this latter dilution had to be increased to 1:60 and, finally, 1:80 due to the high hemolytic activity of some of the sera tested. A buffer red-cell control was used.

The sheep red blood cells were preserved in Alsever's solution prior to use.[36] They were washed twice in 0.15 M saline and finally in Veronal-buffer. A 4 per cent suspension of washed sheep cells in Veronal was mixed with an equal volume of 1:1500 antisheep hemolysin to give a 2 per cent suspension for sensitized sheep red cells (EA). This mixture was then incubated at 37° C for thirty minutes with occasional agitation. A fresh suspension was made daily.

TABLE I. SCHEME FOR MEASURING $C'H_{50}$

Tube	Serum 1:20	Serum 1:80	EA 2%	Veronal
1	0.5	—	0.3	0.7
2	—	0.5	0.3	0.7
3	—	—	0.3	1.2

Final Reaction Volume = 1.5 cc.

A system for measuring the complement activity was set up as shown in Table I, using a final reaction volume of 1.5 cc. The hemolysis was then plotted on log paper against the per cent of light transmitted in a Coleman spectrophotometer set at 541 A°.

Several sera were selected from those showing positive necrotizing activity for complement fractionation (C'1, C'2, C'3, C'4) by the method of Ecker and Pillemer.[9,15,18]

Midpiece (C'1, C'3) and endpiece (C'2, C'4) were obtained by the cold dialysis of 7 cc of serum in dialysis tubing for twenty-four hours on a magnetic stirrer against 4 liters of phosphate buffer (pH 5.4, ionic strength 0.02). The contents of the bag were then centrifuged in the cold and the supernatant (endpiece "E") was drawn off from the precipitate (midpiece "M") and neutralized by the careful addition of 0.1 N NaOH. The precipitate (M) was then washed twice with cold phosphate and dissolved in saline.

Heat inactivated serum (H) was prepared by placing the serum in a 56° C water bath for twenty minutes, thereby, destroying C'1 and C'2.

All final dilutions of the complement components were in the range of 1:2 in respect to the serum. All fractions were tested for their individual hemolytic activity and in combination against previously prepared standards from normal serum to verify their identity and inactivation in a hemolytic system.

The preparation of reagents (R1, R2, R3, R4) each containing all the components except the respective complement fraction,[14,19] i.e. R1 contains C'2, C'3, C'4, and R2 which contains C'1, C'3, C'4, et cetera, was then carried out.

R1 and R2 were prepared by the combination of "H" with "E" and "M," respectively.

Complement lacking C'3 (R3) was prepared by incubating at 37° C for one hour 1.35 mg Zymosan (Lot #5B-171, 100 mg/100 ml saline) with 1 ml of serum taking care to obtain a smooth suspension. The suspension was then centrifuged in the cold and the inactivated serum diluted with saline.

Preparation of R4 by adding 0.25 ml 0.15 N NH_4OH per 1 ml of serum and incubating at 37° C for one and one half hours was done. The solution was then neutralized with 0.15 N NCl.

The reagents (R1, 2, 3, 4) were then injected as described earlier for their necrotizing activity.

Guinea pigs were injected with known necrotizing serum as before. Each guinea pig was then injected subcutaneously with Sandostene®* plus Calcium, an antihistiminic preparation, in doses of 0.1, 0.2, . . . 0.5 cc, respectively, incorporating in each cc 5 mg of the antihistamine and 9 mg of ionized calcium as gluconogalactogluconate.[3,39]

A second series using Sandostene without calcium was followed by first giving the guinea pigs similar doses of antihistamine prophylactically two hours prior to injection of the positive serum.

The results noted, the guinea pigs were then injected with histamine diphosphate in various combinations, as follows: (a) histamine diphosphate in saline; (b) histamine diphosphate in necrotizing serum; and (c) histamine diphosphate in normal serum.

Each of these combinations was then challenged with an antihistaminic preparation prophylactically two hours prior to inoculation and at the time of injection.

A final consideration in the investigation of the necrotizing activity of serum was carried out by preparing guinea pigs with 20 mg doses of injectable hydrocortisone daily for four days prior to injection of known positive serum.

RESULTS

The forty-eight sera used in the study, as shown in Table II, were obtained from patients with a variety of inflammatory diseases and miscellaneous conditions. Of the sera used, twenty-six were from males and twenty-two from females whose ages varied from thirteen to seventy-eight years. Neither age nor sex had any bearing on the presence of a necrotizing factor in the serum. The appearance of necrosis on

*1-methyl-4 amino-N'-phenyl-N'-(2 thenyl)-piperidine tartrate, a product of Sandoz Pharmaceuticals.

TABLE II. $C'H_{50}$ TITERS AND C-REACTIVE PROTEIN VS. NECROSIS

Diagnosis	$C'H_{50}$	CRP	Necrosis (mm)
Anemia (hemolytic)	147	0	0
Appendicitis	182	+++	3
	182	0	0
	196	++	3
Asthma	121	++++	0
Breast tumor (benign)	111	+	0
	98	0	0
Carcinoma (cervix)	98	0	0
Cellulitis (foot)	98	0	2
	197	+++	4
	230	+++	5
Cholecystitis	156	+	0
	136	0	0
Cysticpyelitis	259	++++	0
Cysticpyelitis with renal calculi	278	++++	0
Dermatitis (allergic)	211	+++	5
Dermatitis (generalized)	158	+++	3
Diarrhea (presumed viral)	163	0	0
Diverticulitis	95	0	5
Fever of unknown origin	121	++++	6
Healthy	149	0	0
	172	0	0
	123	0	0
	182	0	0
	170	0	0
Hemorrhoids	109	+++	3
	198	0	0
Intestinal obstruction	193	+++	0
	275	0	5
Lymphoma (neck)	100	0	0
Myocardial infarct (acute)	102	0	0
	259	0	5
Multiple sclerosis	243	+++	0
Obesity (endocrine)	108	0	5
Pancreatitis	121	+	0
Peptic ulcer	95	0	2
Pleurisy	103	+++	0
Pneumonia (unspecified)	206	0	6
	98	0	5
Psoriasis (generalized)	182	0	3
Rheumatoid arthritis	196	+	2
	187	0	0
Salpingitis	173	0	3
Threatened abortion	109	0	3
Thrombophlebitis	138	+	5
Upper respiratory infection	101	0	0
	283	0	0

guinea pig skin could at no time be predetermined by knowing the diagnosis of the patient's illness before injection was carried out. However, while this latter statement held true, it was the knowledge of the presence of inflammation in the greatest percentage of these cases which dictated their selection for the study.

While the $C'H_{50}$ titers of seventeen sera in the list were determined from a 1:40 dilution, rather than 1:80 as were the other complement titers, no correlation could be drawn between these titers, in their respective dilutions and/or to one another, or to the development of a necrotic lesion. And, when present, the degree of necrosis did not appear to be influenced in any way by the complement titer value of the serum. Normal $C'H_{50}$ range equals 120 to 210 when 1/n equals 0.4.[27]

These results, therefore, show significantly that the presence of necrosis in no way parallels the complement ($C'H_{50}$) titer of the serum.

A further review of Table II suggests a correlation between the presence of an acute inflammatory process and the appearance of a necrotizing activity in the serum. However, the presence of such a process

neither necessitates nor predetermines the presence of a necrotizing factor appearing in the serum.

Effect of Serum Complement Components on Necrosis.—Following injection of the complement reagents (R1, 2, 3, 4) the usual twenty-four-hour period of waiting before reading was followed. After this period the injection sites were read for signs of necrosis. At no site of inoculation was there any sign of necrosis developing. An extended period of watching did not change these results in any of the sera fractionated.

TABLE III. EFFECT OF PURIFIED CRP ON GUINEA-PIG SKIN

Guinea Pig	Injected with	Reaction	Remarks
1	CRP plus saline	No necrosis	
2		No necrosis	
3	CRP plus normal serum	No necrosis	
4		No necrosis	
5	CRP plus necrotic serum, neg. CRP	Necrosis	No increase in degree of activity
6		Necrosis	
7	Necrotic serum pos. CRP, adsorbed with CRPA	Necrosis	No decrease in degree of activity
8		Necrosis	

Effect of Time and Temperature on Necrosis.—Sera left standing at room temperature for twenty-four hours or longer lost their necrotizing activity. Complement activity, while diminished, still remained.

Serum placed in a refrigerator at 0° to 4° C kept its activity for at least two weeks, by which time most sera were used. One tube of serum was unintentionally overlooked and still possessed its necrotizing activity for over one month.

Relationship of C-reactive Protein to Necrosis.—Reference to Table II implies a correlation between the presence of CRP in the serum and necrosis. While this is suggestive, no absolute conclusion could be drawn from these results alone.

The absence of CRP in the presence of necrosis, and vice versa in part, suggests what the final conclusion of the role of this protein might be.

The effect of injections of purified CRP alone and in combination with various sera is summarized in Table III. Not only did the addition of CRP or its removal (Table III, guinea pigs 5 to 8, inclusive) leave the necrotic activity unaltered but, the lesions were relatively unaffected in size.

Effect of Antihistaminic Preparations and Histamine.—Sandostene-Calcium and Sandostene Tartrate used as the inhibiting agents were injected both prophylactically and at the time of serum inoculation. Neither of these antihistaminic preparations inhibited the development of necrosis in their respective series.

On one occasion each, doses of 0.2 cc and 0.3 cc (1.0 and 1.5 mg Sandostene-Calcium, respectively) appeared to inhibit the development of a lesion. However, repitition of these dosages and serum of the same patient failed to show the same results on other guinea pigs.

Whether these animals were refractory to that specific serum was not determined. However, in the light of the reproducible negative results, it was felt to be of little consequence.

TABLE IV. EFFECT OF HISTAMINE DIPHOSPHATE AND ANTIHISTAMINICS** ON NECROSIS

No. of Guinea Pigs	Injected with	Reaction
2	Normal serum plus antihistamine	No Necrosis
10	Necrotizing serum plus antihistamine	Necrosis
12	Histamine in saline	Wheal early, no necrosis
	plus antihistamine	No necrosis
12	Histamine in normal serum	Wheal early, no necrosis
	plus antihistamine	No necrosis
12	Histamine in necrotizing serum	Wheal early, necrosis in 24 hours
	plus antihistamine	Necrosis

**Both antihistaminic preparations in all dosages at the time of and two hours prior to serum inoculation

The addition of histamine diphosphate to the study, as summarized in Table IV, led to similar results.

Effect of Corticosteroid Hormone on Necrosis.—Preparation with hydrocortisone in no way inhibited the development of a lesion, and the size of the lesion was unchanged, essentially, from those used for control.

DISCUSSION

Although, the original studies only implicated complement with the necrotizing factor of serum, it seemed the most likely point of departure to first investigate complement and its properties.

Complement has been implicated as an inhibiting substance in the serum of rheumatoid arthritis (R-A) as studied in the R-A sheep red cell agglutination test.[41] Also, its possible role in causing necrosis[4,23] made the study of the complement of these sera a good likelihood in finding the causative agent of necrosis in guinea pig skin.

Since the earliest studies on the sera of freshly drawn blood for their cytolytic property, one can find many conflicting statements as to the properties of complement. The destruction of complement by heat, its disappearance from serum on long standing, and its sensitivity to other reagents and variables, in part explain the confusion which exists over this factor of serum.[9,15-17,31,43]

Heidelberger et al,[15,19] employing the rigorous criteria of analytical

chemistry, found that less than 1 per cent of the total serum proteins of guinea pigs comprises the protein portion of complement, suggesting further the difficulties encountered by investigators in determining its chemical and biophysical properties.

Pillemer[43] and Hegedus[14] showed how complement fractionation could be carried out and then titrated for in a hemolytic system. Why then could not these techniques be used to determine wherein the necrotizing characteristic of serum lay? With this latter intention, the fractionation and injection of the complement components were done.

The negative results of this work are significant in the light of all the attention complement is receiving in current literature. The lack of correlation between complement titers and necrosis is of less significance than the inability to find in which fraction of the complement this activity is possessed.

The author is well aware of the long procedure which fractionation of complement entails. Hence, the fact that these long methods bring about the removal of the necrotic characteristic only reaffirms the conclusion that, while this very unstable factor, complement, can be maintained, necrosis is lost and therefore is not a property of complement.

Other complement fractions have been studied by Libretti et al[27] and Brumfield.[5] However, why then without their removal are they not active in bringing about necrosis despite the removal of their less stable cousins?

The consideration must then fall to another serum factor if the necrotizing substance or substances are to be found. The rationale for the introduction of the C-reactive protein as outlined briefly, earlier in this paper, seems then to be an important consideration.

The CRP factor, an abnormal protein appearing between the alpha-2 and globulin fraction[33] of "acute phase" serum, is a sensitive indicator of inflammation. The occasional presence of CRP in cancer[42] and in acute myocardial infarction,[22] among others, suggests a nonspecific type response of serum to inflammation. This latter role upon consideration might, likewise, be attributed to the necrotizing factor of the serum.

The results of the original test for CRP on the whole serum (Table II) do not conform in all instances with what might be expected. In regard to the latter therapy prior to admission to the hospital could well have interfered with the presence of the CRP in some of those sera in which one might expect its presence. The correlation in Table II between CRP and necrosis might have been greater had none of the patients received prior medication.

If, however, therapy removes or inactivates the CRP, as it does in rheumatic fever, so that it is essentially no longer present, the existence of necrosis in view of a negative CRPA test implies that this factor, likewise, is not the necrotizing substance in serum. In fact, had no

therapy been used on any of these patients, any correlation arrived at would have been a false interpretation.

The acceptance of this hypothesis is made valid when the further employment of purified CRP and its combination with various sera was carried out (Table III) and proved to substantiate this belief.

What else could this factor be? Lovell showed that this was not a reaction to a Forssman antibody,[8] although the lesions caused by the sera were quite similar in appearance histologically.

Menkin's[35] studies on inflammation have uncovered a substance which he named "necrosin" for its systemic necrotic potency when introduced intravenously. This factor while thermolabile is, however, not lost on dialysis as is the necrotizing substance of "acute phase" serum.

Was necrosis then brought about by a histamine release in the tissue, once it was stimulated by these sera? This question seemed next in line to be answered.

Allergists have devoted much study to skin testing and the disposition of these injected sites. Therefore, little need be said about the erythema, pseudopods and wheals which develop when histamine is released.[46]

The results of this study seem to be an adequate discussion as to the role of histamine in necrosis. The lack of inhibition of the lesion by antihistamines may be disputed on the basis of dosages used, but the histamine controls with their negative results are significant. The necrotizing serum, furthermore, is one which essentially affects capillaries and veins, bringing about their dilatation, formation of mural thrombi with diapedesis of blood cells, and the coagulative necrosis of proximate muscle fibers. These tissue changes, while they are nonspecific, are not recognized as the typical reactions of a shock tissue to an allergen.[2] Yet, these responses are reproducible each time a necrotizing serum is used on the same or different guinea pigs. It seems, thereon, that one might justifiably conclude along with the other results that this is not a histaminic effect.

The action of corticosteroids on inhibiting the local tissue reactivity response to inflammation is in itself a detailed study.[6,34,40] It, therefore, was the desire of this study to include the corticosteroids empirically with no intention of drawing any conclusions in the vast field of endocrinology, in an additional attempt to learn the nature of the necrotizing substance. Lovell was unable to inhibit the reaction in his guinea pigs with 25 mg doses of cortisone daily for five days. He showed, in addition, that several of his patients receiving unspecified doses of this hormone still had a necrotizing activity in their sera.

The use of hydrocortisone in 20 mg doses, despite its greater strength over cortisone, in this study proved to have no different effect.

CONCLUSION

While this study has not determined the etiology of the necrotizing potency in "acute phase" serum, it has shown what it is not.

The necrotizing substance is not complement nor any of its fractions, as tested for in a hemolytic system. Nor, is it C-reactive protein or histamine.

This study was submitted, however, with the hope that, in increasing our knowledge of the processes of inflammation, these negative results may play a positive role.

SUMMARY

1. Guinea pigs were injected intradermally with whole serum of patients with a variety of acute inflammatory conditions.

2. All sera were tested for their complement titers and presence of C-reactive protein.

3. Studies were then done on those sera which caused necrosis of guinea-pig skin in relation to: (a) complement components; (b) C-reactive protein; (c) histamine and antihistamine; and (d) effect of corticosteroid hormones on the development of the lesion.

4. None of the above substances was found to be, or to alter, the necrotizing factor of "acute phase" serum.

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SPECIFICITY OF THE ANAPHYLACTIC READING

The anaphylactic reaction has enabled us to determine the human or animal nature of mummies many thousands of years old. We may remark that the precipitin reaction as well as that of fixation of complement proved ineffectual in these cases.

What is of more direct utility is the fact that the anaphylactic reaction can be employed with success in the examination of the products of secretion and excretion, such as milk, egg-albumen, haemoglobin, gastric juice, sweat, oils, et cetera.

In certain cases, it supplies information as to specificity where precipitins fail; in that of crystallins, for example.

Karl Schern has employed the anaphylactic reaction to discover adulteration of earth-nut oilcakes with rice grains, field mustard, et cetera.

Minet and Leclerq have carried out interesting experiments on sausages manufactured from different kinds of meat—veal, pork, and horse-flesh. They sensitized guinea pigs with macerations of these different kinds of sausages; then, some time afterwards, they submitted the guinea pigs to the intravenous test with sera from veal, pork, and horse-flesh. They demonstrated the fact that so long as one is dealing with the meat of a single species sensitization takes place on normal lines and specificity appears to be complete. But when one is in the presence of a mixture of several kinds of meat, sensitization ceases to take place regularly.—Dr. A. Besredka, Anaphylaxis and Anti-Anaphylaxis and their Experimental Foundations. (1919.)

THE PREVENTION OF REACTIONS TO REPOSITORY INJECTION TREATMENT

ETHAN ALLAN BROWN, M.R.C.S., England, L.R.C.P., London
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AN EXAMINATION of the data recently published by Loveless[1] demontrates that repository (single injection) therapy for ragweed pollenosis is not only feasible but equal in its results to multiple injections of aqueous extracts of the same pollen. She reports, however, an incidence of overdose reactions in 5.2 per cent of 117 patients given 441 repository injections. (This is the same percentage as that occurring in patients receiving aqueous extract.) The percentage could be expected either to be greater because of the large dose given or to be smaller because the concentrated extract is injected in emulsion form. Loveless used no prophylactic measures to avoid reactions. If the repository type injection, which otherwise has so much to recommend it, is, as well, to be practical in general clinical allergy, some method of preventing or diminishing such reactions must be found.

The present report describes pretreatment measures taken to prevent anaphylactic reactions in thirty-seven of thirty-eight patients given repository injections. One additional patient, not given such pretreatment, reacted with urticaria and coryza.

Randomization was assured by treating patients in succession as they routinely presented themselves preseasonally, as either new patients seeking treatment or else as patients taking a course of conventional aqueous injections and independently of the level of treatment reached or the results as measured by clinical response in those patients under treatment for more than one year.

Two patients treated, for several reasons, differently from the others will be discussed first. One patient received a repository injection of 4,500 Protein Nitrogen Units and another of 5,000 units.

The one patient given 4,500 P.N.U. had responded to an intracutaneous test of 2000 P.N.U. with a typical wheal and pseudopodia, (a three plus reaction). She had taken conventional treatment with aqueous extracts since April 16, 1957, having reached a subcutaneously injected dose of 80 P.N.U. Despite a clinical history of twenty years of fall pollenosis, her ophthalmic test was negative at the 10,240 P.N.U. level.

The one patient given 5,000 P.N.U. had never previously been skin tested or given injection treatment for three seasons of typical ragweed pollenosis. He responded to a pressure-puncture test with a typical wheal and pseudopodia. His ophthalmic test at the 20 unit level was positive. Confirmatory tests at the 40, 80 and 160 unit levels not only caused conjunctival injection and redness of the caruncle but sneezing and copious coryza.

Twenty-two patients were given injections of the repository type, the dose being 7,500 P.N.U. The complete range of their randomization is shown by the fact that four had never previously received injection treatment. Three more had had conventional treatment; one, in 1950, one in 1949 and one in 1937.

Of the fifteen, one had recently received subcutaneously 0.5 P.N.U.; one, 15; three, 30; one, 60; one, 200; three, 600; one 1000; one, 1200; one, 5000; one, 5500; and the last 7000 P.N.U.

The conventional skin test reactions of these twenty-two patients varied greatly. Nine had responded to pressure-puncture tests so markedly that no intracutaneous tests had ever been done.

Five of these patients with pressure-puncture positive skin tests reacted at the 40 P.N.U. ophthalmic test level. Interestingly enough, a patient who reacted with a large pressure-puncture test in 1954 and who had successfully taken aqueous injection treatment responded negatively to an ophthalmic test at the 10,240 P.N.U. level. Another, who had shown a pressure puncture positive skin test in 1956 and who had presented no symptoms since, was equally negative to 10,240 P.N.U. used ophthalmically. But one patient, markedly clinically sensitive, needed only 80 units to elicit an ophthalmic positive test. The ninth patient responded at the 160 P.N.U. level.

There were five patients who gave positive intracutaneous tests with the 100 P.N.U. solution. One, a "transition patient" treated with excellent results since 1946, did not respond with a positive ophthalmic test to 10,240 P.N.U. One who had not been tested by the pressure-puncture method but gave an eight plus reaction (wheal 2.5 cm) and who had responded to treatment with fair results reacted ophthalmically to 320 P.N.U. One with a four plus reaction (wheal 1.5 cm) responded ophthalmically to 80 P.N.U. and two to 160 P.N.U. All had not responded well to conventional treatment. In this group, eye tests and clinical symptoms could be correlated to a satisfactory degree.

Of the next group of reacting patients, six tested intracutaneously with 1,000 P.N.U. showed one who had given a one plus reaction in 1956 and who had done exceedingly well. He did not respond to 10,240 P.N.U. applied to the eyeball. Another, a five plus reactor dermatologically, responded ophthalmically to 40 P.N.U. and two others, four plus reactors, needed 160 P.N.U. for positive ophthalmic tests. Still another, with the same size skin test, reacted to 320 and the last to 640 P.N.U. All had needed some supplementary medication.

Two patients who gave positive tests to 2,000 P.N.U. intracutaneously were again consistent. One had received conventional injection treatment since 1952 and the other since 1954. Both were in transition from aqueous to repository injection treatment. Both failed to react to the 10,240 P.N.U. ophthalmic test solution.

It appears that if we can postulate that the pressure-puncture and intra-

cutaneous tests had been used in serial dilutions as they were with the ophthalmic tests, greater consistency between the intracutaneous and the ophthalmic tests and clinical sensitivity might be measurable, but the variable of clinical reaction is too difficult to define. There appears to be no doubt, however, that in this small series the ophthalmic test mirrored the clinical sensitivity much more consistently than did the pressure-puncture or intracutaneous tests.

Fourteen patients received a repository injection of 10,000 P.N.U. Of these, two had had no previous injection treatment. The range of dosage of the aqueous injections for the others was as follows: one, 1 P.N.U.; one, 40 P.N.U.; one, 300 P.N.U.; one, 400 P.N.U.; one, 520 P.N.U.; one, 600 P.N.U.; one, 900 P.N.U.; one, 1000 P.N.U.; one, 4000 P.N.U.; two, 4500 P.N.U.; and the last went from 6000 P.N.U. aqueous to the 10,000 P.N.U. repository injection. As in the previous group of patients, repository injections were based on the responses to the ophthalmic test.

Three had previously presented pressure positive skin tests. Of these, the first had so reacted in 1951 and with conventional treatment had done extremely well with no symptoms since. His ophthalmic test was negative at the 10,240 P.N.U. level. The second, who had done well, although his pressure-puncture test was similarly positive in 1955, also did not react to the ophthalmic 10,240 P.N.U. level. But the third, with a positive pressure-puncture test in 1954 and some symptoms each year since, while on conventional treatment gave a positive reaction at the ophthalmic 1,280 P.N.U. level.

Two "transition patients" who, in 1945 and 1946, responded typically to intracutaneous tests and who had presented no symptoms for many years, both failed to react ophthalmically to 10,240 P.N.U. A sixth, whose skin test reaction was positive to 2,000 P.N.U. in 1952 and who had done well, also failed to react to 10,240 P.N.U. applied to the conjunctiva. But, a seventh patient, who in 1954 reacted typically to the intracutaneous test but who had presented some symptoms each year since, reacted positively to 5,120 P.N.U. applied ophthalmically.

Of five more who did not react to 10,240 P.N.U., the first had given a three plus reaction in 1954, the second and third had so reacted in 1956 and the last two in 1957.

A patient who had taken treatment since 1954 by conventional methods and had not responded well, reacted at the 1,000 P.N.U. skin test level with a four plus reaction, and to 1,280 P.N.U. ophthalmically. The last with a fairly good but not complete clinical response to conventional treatment taken since early 1956 gave a two plus reaction to 2,000 P.N.U. used intracutaneously, but responded with a positive test to 2,560 P.N.U. ophthalmically.

In this small group of fourteen, the five patients with symptoms gave consistent positive ophthalmic tests and those with no symptoms failed to respond to 10,240 P.N.U. It would appear that the stronger the solution

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Date: 6/12/57

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75 BAY STATE ROAD, BOSTON, MASS.
REPOSITORY THERAPY

Diagnosis: H F

Previous Rx: None

Previous S.T.: None ; 6/12/57 Ragweed P.P. - markedly positive

Pre-Repository Medication: Chlor-trimeton Repetabs 8 mgs ; 0.3 cc Sulphrine 10:00 A.M.

Post Repository Medication: Perazil

Antigen: Ragweed

Group: 40 - 240 P.N.U./cc End point: 40 PNU ; Total Dosage: 7500 PNU.

TIME	CONCENTRATION	REACTION	AMOUNT	B/P	PULSE
9:30 AM				130/90	100
		Ophthalmic Tests			
9:35	10 PNU/cc	1/2	1 drop		
9:40	20 PNU/cc	1/2 - 3/4	1 drop		
9:45	40 PNU/cc	1	1 drop		
9:50	80 PNU/cc	2 ± swollen eye l.d	1 drop		
10:00				130/80	100
10:15				134/80	96
		Repository Therapy			
10:25	1000 PNU/0.1 cc		0.2 cc	130/80	96
10:30				130/80	96
10:35				130/80	96
10:40				130/80	108
10:45				110/70	130
10:50				120/80	120
10:55	1000 PNU/0.1 cc		0.25 cc	120/80	100
11:00				120/80	100
11:05				120/80	108
11:15				130/80	104
11:25	1000 PNU/0.1 cc		0.3 cc	130/90	104
11:35				134/80	104
11:45				130/90	104
12:00				130/90	108
12:05 PM				120/80	100

Name: Colombo, Catherine
No. 4728
Date: 6/11/57

DR. ETHAN ALLAN BROWN
M.R.C.S. ENGLAND L.R.C.P. LONDON
75 BAY STATE ROAD, BOSTON, MASS.
REPOSITORY THERAPY

Diagnosis: B.A. H.F.

Previous Rx: None

Previous S.T.: Ragweed P.P. markedly positive

Pre-Repository Medication:

Post Repository Medication: Diafen

Antigen: Ragweed

Group: 40 - 240 PNU/cc End point 40 PNU Total Dosage: 7500 PNU.

TIME	CONCENTRATION	REACTION	AMOUNT	B/P	PULSE
10:00 AM				120/80	84
		Ophthalmic Tests			
10:05	10 PNU/cc	Negative	1 drop		
10:10	20 PNU/cc	1/2	1 drop		
10:15	40 PNU/cc	1	1 drop		
10:20	80 PNU/cc	2 - hole 3 stuffy	1 drop		
		Repository Therapy			
10:50	1000 PNU/0.1 cc		0.2 cc	120/80	80
10:55				120/80	80
11:00				110/70	80
11:05				110/70	84
11:10	1000 PNU/0.1 cc		0.25 cc	120/80	84
11:15				120/80	88
11:20		1 sneeze		120/70	100
11:25		1 sneeze		130/80	96
11:30				120/80	96
11:35				130/80	100
2:00 P.M.	1000 P.N.U./0.1 cc		0.3 cc	140/80	120
2:05				130/80	120
2:10				130/80	104
2:20		2 sneezes		130/80	120
2:45		2 sneezes - twitching nose & scratchy throat		120/80	100

required for positive skin tests, the stronger the concentration needed for positive reaction of the conjunctiva. The apparent inconsistencies are due, in part, to our randomization of "transition patients." We have, for instance, no data for all of the intervening years.

One patient, first seen in 1945, responded with a three plus reaction to 100 P.N.U. in that year and in 1952, with the same-sized reaction, to 1,000 P.N.U. In 1957 her skin test reaction to 2,000 P.N.U. was negligible. Symptoms occurred during the ragweed seasons of 1953, 1954 and 1955. There were no symptoms during 1956 and none had appeared by September 23, 1957.

Another of the patients who had responded with a three plus positive reaction to a 100 P.N.U. test in 1946 and again with a negligible reaction to 1,000 P.N.U. in 1952, reacted with three plus to 1,000 P.N.U. in 1955, 1956 and 1957, although there was a negative ophthalmic test. He has suffered no symptoms from September 28, 1948, to September 23, 1957.

Loveless' reported reaction rate of 5.2 per cent might be acceptable during initial studies but might be a formidable obstacle to the use of the repository method in private practice. We undertook to inject the patients described with single doses of 4,500; 5,000; 7,500 and 10,000 P.N.U. of the material furnished by Loveless.

Ancillary studies consisted of a physical examination with blood pressure determinations and timed vital capacity pulmonary function assays. A urinanalysis and complete hemogram, with blood smear, blood sedimentation rates and blood serology tests were done, for new patients at the time of the injection, and for "transition patients" either at the same time or some time during the previous twelve months.

As soon as the ophthalmic test level was determined and independently as to whether it was positive or negative, each patient was given Sus-Phrine® (0.3 cc) subcutaneously, and by mouth, a tablet of chlorprophenpyridamine, 8 mg (Chlor-Trimeton Repetab® coating, 4 mg and core 4 mg).* In several patients other antihistaminic agents were administered. Twenty minutes later, an examination of the pulse usually proved it to have accelerated.

Loveless uses the accelerated pulse as an indication of impending reaction, since an increase in pulse rate and a rise in blood pressure both usually precede anaphylactic shock. We knew that the delayed-action type of epinephrine would accelerate the pulse and raise the blood pressure, but we considered the response before the repository injection had been given as proof that the patient was under the influence of the epinephrine. In those patients who might react anaphylactically despite the epinephrine, we expected a second increase in pulse rate and blood pressure.

The repository injection material was arbitrarily divided usually into three but sometimes into four or five parts, injected at fifteen to twenty

*Sus-Phrine® is a product of Brewer and Company; Chlor-Trimeton® is a product of Schering Corporation.

minute intervals into the exact same site using the same skin puncture and inserting the needle at the same angle, so that the injection material was placed as skill permitted into the center of the same globule of emulsion. Proof that this could be done was demonstrable by tactile examination, a single globule usually being felt.

The reproductions of actual laboratory sheets for two typical patients illustrate the sequence of events.

The patients remained in the office approximately one hour after the last part of the injection had been given. They were then issued six tablets of the antihistaminic agent to take: one on arising, one at 2:00 p.m. and one at bedtime for the two following days, to lessen any delayed reactions that might occur.

The data of one patient not given delayed action epinephrine but instead Diafen® 2 mg (diphenylpyraline hydrochloride)** scheduled every six hours is shown on the first reproduced history sheet. At 8:00 p.m. of the day of treatment she presented a generalized urticaria and moderately severe nasal symptoms. Her husband, a physician, injected Solu-Cortef®† intravenously on two occasions one hour apart. This was followed by an immediate remission, but scattered, transient, nonpruritic urticae appeared during the following morning. There was no local reaction. Postseasonally, the patient reported some days of mild symptoms and three days of moderate symptoms requiring, however, no medication. Her symptoms for the mild 1956 pollen season required continuous Meticorten ®‡ therapy.

The second patient who reacted adversely did receive delayed action epinephrine. He telephoned at 5:00 p.m. of the following day because he had suffered a generalized pruritus followed by a nonpruritic rash. There was profuse perspiration and a productive cough, but no bronchospasm. These symptoms lasted from 2:00 p.m. to 4:00 p.m. The patient took his bedtime dose of the antihistaminic agent with resulting drowsiness. He reported that his symptoms were not as severe as during 1956. Sneezing began in mid-August and lasted until September 7. The patient lost no time from work as he had during previous years. No other patients reported adverse reactions.

The results of the repository injection treatment of the remaining patients will be published soon after they have been subjected to statistical analysis.

In summary, thirty-eight patients received repository injection treatment consisting of 4,500, 5,000, 7,500, and 10,000 P.N.U. given in divided doses over a period of one hour, only one injection site being used.

One patient, not pretreated with delayed action epinephrine but given instead a mild antihistaminic agent (Diafen®), responded with urticaria five hours later. One patient given pretreatment epinephrine and an anti-

**Diafen® is a product of the Schenley Company.
†Solu-Cortef® is produced by The Upjohn Company.
‡Meticorten® is a product of the Schering Corporation.

histaminic agent (Perazil®)* suffered pruritus followed by a nonpruritic rash.

Thirty-six other patients, pretreated with delayed action epinephrine (0.3 cc) and delayed action chlorprophenpyridamine (8 mg), of whom seven had either never or in recent years taken conventional injection treatment, took repository injections of the magnitude given with no reactions whatsoever.

It can tentatively be concluded from this initial study of a small group of patients that the prophylactic treatment described may possibly lessen the number or minimize the degree of reactions to the repository type of injection. It can, however, also be concluded that patients suffering from pollenosis are capable of absorbing, without reaction, much larger doses of pollen extract than had previously been considered safe.

ADDENDUM

To save space, all discussion of the immunological relationships known to exist in treated and untreated patients tested ophthalmically and intracutaneously has been omitted, so that more data concerning positive and negative skin and eye tests could be described in relation to injection doses.

ACKNOWLEDGMENT

The invaluable assistance of Miss Evangeline Chumacas, Miss Gloria Guarino, and Miss Patricia Pepin in the preparation of this paper is gratefully acknowledged.

REFERENCE

1. Loveless, M. H.: Repository injection in pollen allergy. J. Immunol., 79:10, 1957.

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*Perazil® is a product of Burroughs Wellcome and Company.

THE DESCRIPTION AND ANALYSIS OF MOOD

We have used human subjects, but good experimental work with complex human behavior—involving, as it does, incomplete control of the subject, his life history, and his environment—is difficult, tantalizing, and frustrating. We often wonder if there must always be an inverse relationship between the magnitude and importance of a problem in behavioral science and the adequacy of the scientific methodology by means of which it can be attacked. The rapidly growing list of publications on drugs and human behavior attests to the wide interest in and need for research in this area, but it leaves much to be desired from the point of view of methodology. Those of us who are rash enough to investigate these problems at the human level usually find that whenever we succeed in getting certain variables under reasonable control we merely highlight the importance of still other variables.—VINCENT NOWLIS and HELEN H. NOWLIS (Ann. New York Acad. Sc., 65: 345, 1957).

CLINICAL EVALUATION OF SANDOSTENE® PLUS CALCIUM IN BRONCHIAL ASTHMA

Spirometric Studies

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THE TREATMENT of bronchial asthma continues to pose a difficult problem in medicine, especially in chronic cases in which pulmonary emphysema has developed. Agents commonly employed in the treatment of asthma, such as the anticholinergic, adrenergic and xanthine drugs, often fail to bring satisfactory relief in such patients. In addition, these agents may produce side effects or reactions which run counter to the desired therapeutic effect.[9,13] The use of steroid hormones for sustained treatment is often disappointing,[3,4,12,15,21] and often dangerous.[11,19]

Unquestionably, a need exists for an effective and nontoxic agent for the treatment of patients with inadequately controlled bronchial asthma. The pharmacologic properties of Sandostene® (1-methyl-4-amino-N'-phenyl-N'-(2-thenyl)-piperidine tartrate) meet the requirements for such an agent, especially when combined with calcium (Neo-Calglucon) in the preparation, Sandostene + Calcium.

Sandostene has been shown to exhibit a marked antagonism to histamine and acetylcholine, as well as demonstrating an unusually potent inhibitory effect of vascular permeability.[1,5,3,18,20,22,23] Moreover, numerous studies have revealed that it is well tolerated[1,5-8,10,22,23,24] and that these properties are strongly enhanced when combined with calcium.[3,18,20,23,24] This has been shown in the experimental animal and in human studies.

A preliminary trial of this preparation was undertaken in fifteen patients with bronchial asthma and chronic emphysema, who had not responded to previous treatment. When eleven of these volunteered the information that they had obtained distinct relief, we were encouraged to institute an objective study to determine more accurately its use in the treatment of bronchial asthma with chronic emphysema.

The most common spirometer tests were chosen, i. e., the measurement of maximum breathing capacity (m.b.c.) and total vital capacity (t.v.c.). Since most recent reports[13,14,25,27] consider the timed vital capacity to be more reliable than the t.v.c., the two-second value of the vital capacity was also determined. Further, a new test, the "respiratory index" (RI) by Gross,[17] which has been described as useful in the evaluation

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Presented at the Thirteenth Annual Congress of The American College of Allergists, Chicago, Illinois, March 20, 1957.

of chronic pulmonary diseases,[23] was also performed. (RI=t.v.c. expressed in units of 100 cc + breath-holding time in seconds). The latter test was included to determine its correlation with the above-mentioned measurements.

METHOD AND MATERIAL

Patients were selected from the Outpatient Allergy Clinic of Mount Sinai Hospital, Chicago, Illinois. A careful case history was taken and a general physical examination was performed. Only patients with clinically manifest signs of bronchial asthma and chronic emphysema were included in these studies. If a cardiac complication was suspected, an electrocardiogram was ordered. The patients were divided into two groups according to heart status: (1) patients with clinically normal cardiac function, and (2) patients with a cardiac component. The shortness of breath of the latter group was ascribed partly to bronchospasm and partly to the cardiac factor. Of the thirty-four patients, nineteen were found to belong to the first group and fifteen to the second group. These groups were again subdivided by sex.

The spirometer tests were performed on a simple water spirometer.* The vital capacity and the maximum breathing capacity were expressed in liters of air at room temperature, wet, ambient pressure. For the maximum breathing capacity, an interval of eleven seconds was used and the results were expressed in liters per minute. The breath holding time test was performed according to Gross.[17] Predicted values of the maximum breathing capacity and the vital capacity were calculated according to age, sex, height and weight.[2] For the calculation of the timed vital capacity, a two-second interval was measured off the final record. In this range neither the curve of the asthmatic patients nor that of normal volunteers was found to be too steep for a correct determination. According to Gaensler, [13] after two seconds, 94 per cent of the total vital capacity was considered to be normal.

The testing procedure was kept uniform. After instruction, a control test, which was not evaluated, was performed. This method was used in order to teach the patient and acquaint him with the procedure. Each test was performed twice before and twice after the administration of the drug. The largest measurements were evaluated. If a difference of more than 10 per cent between duplicate determinations was observed, the test was discarded. The sequence of the single tests was: first, total vital capacity; second, breath-holding time; third, maximum breathing capacity. After each performance, the patient was allowed to recover for ten minutes. An interval of twenty minutes was allowed after administration of the drug. Only one drug was given to an individual patient

*Warren E. Collins, Inc., Boston 15, Massachusetts.

on any one day. Only patients with active symptoms of bronchial asthma were used in this study.

Pulse frequency and blood pressure readings were taken before these respiratory function tests. Subjective side reactions after drug administration were noted. Furthermore, the patients were directed to report their subjective feelings during the twenty-four hours following the drug administration. The following drugs were employed in all cases:

Theophylline ethylenediamine—"Aminophylline"	20 cc	500 mg	intravenous
Epinephrine	0.5 cc	0.5 mg	subcutaneous
1-methyl-4-amino-N'-phenyl-N'-(2-Thenyl)-piperidine tartrate (Sandostene)	10 cc	50 mg	intravenous
Neo-Calglucon (Calcium Gluconogalactogluconate)	10 cc	1.37 Gm	intravenous
Sandostene		50 mg	
+	10 cc		intravenous
Calcium		1.37 Gm	
Physiologic saline solution	10 cc	...	intravenous

RESULTS

The results were calculated separately for each of the following four groups, and compared:

Patients with bronchospasm and pulmonary emphysema with normal cardiac function		
Group I	male	12 patients, aged 21 to 66 years
Group II	female	7 patients, aged 13 to 61 years
Patients with an additional cardiac component		
Group III	male	7 patients, aged 42 to 78 years
Group IV	female	8 patients, aged 32 to 65 years

Maximum Breathing Capacity (m.b.c)

Group I

Before drug administration, the average value of the m.b.c. in this group was 45.7 1/min., or 33.6 per cent of the predicted value. The highest value was 60.0 1/min (42.6 per cent), the lowest 26.8 1/min (24.6 per cent).

Changes of the m.b.c. after drug administration:—The increase is considered to be significant when it is greater than 20 per cent of the predetermined value or more than 10 1/min.[8]

(a) Aminophylline (Am):—The average m.b.c. increased from 45.5 l/min to 64.6 1/min or from 33.4 per cent to 47.6 per cent of the predicted value. The highest m.b.c. before aminophylline was 59.4 1/min (41.0 per cent), the lowest was 28.0 1/min (25.7 per cent). After aminophylline, the values were 75.5 1/min (53.5 per cent) and

38.8 1/min (35.9 per cent) respectively. The greatest increase was 32.4 1/min, the smallest 10.8 1/min. Aminophylline produced in all the patients of group I a significant increase of the maximum breathing capacity.

(b) Epinephrine (Ep):—The increase of the average values was only slightly smaller, namely from 46.1 1/min, or 33.8 per cent, to 64.3 1/min, or 47.4 per cent respectively. The greatest increase amounted to 38.8 1/min, while the smallest increase was 3.4 1/min. In three cases, the increase cannot be considered significant.

(c) Sandostene + Calcium (Sst + Ca):—The average increase was slightly smaller than the increases achieved with aminophylline or epinephrine. The pertinent determinations amounted to 46.2 1/min (33.9 per cent) before and 63.7 1/min (46.9 per cent) after the drug was given. The greatest increase was 29.7 1/min, the smallest 8.8 1/min. The increase was significant in eleven of the twelve cases.

(d) Sandostene (Sst):—Sandostene alone was considerably less effective than Sandostene + Calcium (Sst + Ca). The average m.b.c. increased only from 46.0 1/min (33.8 per cent) to 51.5 1/min (37.9 per cent). The greatest increase was 10.5 1/min, and in one case even a small drop of 1.3 1/min was observed. In only three cases was a significant increase achieved.

(e) Neo-Calglucon (Ca):—The changes in the m.b.c. demonstrated with Ca were, as expected, small, and in no case significant.

(f) Physiologic saline solution (Sal.):—Here, in one case, a drop of 8.8 1/min was observed. This decrease amounts to 19.2 per cent of the predetermined m.b.c., and may perhaps be related to the stress of the test. All the other individual changes, as well as the change of the average value, were insignificant.

Group II

The m.b.c. before any drug or placebo was given ranged here from 48.7 1/min to 20.4 1/min, or from 50.8 per cent to 27.9 per cent of predicted value. The average was 36.0 1/min (39 per cent).

Changes of the m.b.c. after drug administration:—Aminophylline again produced the greatest increase above the average values, and in all seven patients the increase was significant. The average increases obtained with epinephrine and Sandostene + Calcium were progressively smaller. Epinephrine failed to improve the m.b.c. significantly in one of the seven cases. As to the increases achieved with Sandostene + Calcium, these were significant in all cases. Sandostene without calcium produced a significant increase in only one case. No significant change was observed with calcium or with physiologic saline solution, with the exception of

TABLE I. CHANGES OF THE M.B.C. AFTER DRUG ADMINISTRATION. PATIENTS WITH NORMAL CARDIAC FUNCTION

	Am		Ep		Sst+Ca		Sst		Ca		Sal	
Group I — 12 Patients	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Average—1/min.	45.5	64.6	46.1	64.3	46.2	63.7	46.0	51.5	45.9	46.6	45.1	43.5
Average per cent of prediction	33.4	47.6	33.8	47.4	33.9	46.9	33.8	37.9	33.6	34.1	33.2	32.0
Max. increase 1/min.	—	32.4	—	38.6	—	29.7	—	10.5	—	6.4	—	6.1
Min. increase (max. decrease) 1/min.	—	+10.8	—	+ 3.4	—	+ 8.8	—	− 1.2	—	− 5.7	—	− 8.8
Significant increases	—	12	—	9	—	11	—	3	—	0	—	0
Group II — 7 patients												
Average 1/min.	35.7	49.3	35.6	48.4	36.0	47.5	35.3	38.9	37.2	36.7	36.0	36.5
Average per cent	38.6	53.6	38.6	52.6	39.0	51.6	38.2	42.3	40.1	39.6	39.0	39.4
Max. increase 1/min.	—	19.3	—	20.7	—	13.0	—	7.3	—	4.4	—	4.8
Min. increase (max. decrease) 1/min.	—	+ 8.2	—	+ 3.8	—	+ 9.3	—	+ 1.4	—	− 3.0	—	− 4.0
Significant increases	—	7	—	6	—	7	—	1	—		—	0

TABLE II. CHANGES OF THE M.B.C. AFTER DRUG ADMINISTRATION. PATIENT WITH A CARDIAC FACTOR

	Am		Ep		Sst+Ca		Sst		Ca		Sal	
Group III — 7 patients	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Average 1/min.	27.9	37.7	29.0	34.8	28.7	40.2	29.7	34.1	29.7	29.2	29.1	27.3
Average per cent of prediction	27.0	36.2	27.8	33.5	27.7	38.9	28.6	33.0	28.6	28.3	28.1	26.3
Max. increase 1/min.		18.7		12.8		13.2		7.4		4.9		3.7
Min. increase (max. decrease) 1/min.		+ 4.2		− 1.9		+ 8.7		+ 2.9		− 5.1		− 3.9
Significant increases		6		3		7		1		0		0
Group IV — 8 patients												
Average 1/min.	27.0	34.0	26.8	31.7	27.9	36.1	26.5	29.1	26.5	25.6	26.6	25.3
Average per cent of prediction	32.3	40.7	32.1	37.9	33.4	43.5	31.7	34.7	31.7	30.6	31.9	30.2
Max. increase 1/min.		9.4		9.1		9.8		4.4		2.4		1.4
Min. increase (max. decrease) 1/min.		+3.9		+1.2		+6.4		− 1.1		− 3.8		− 3.3
Significant increases		6		2		8		0		0		0

three cases where drops of 12.7 per cent, 13.0 per cent and 17.7 per cent of the predetermined value occured. This, perhaps, points to an aggravation.

Table I records the values obtained in groups I and II.

Group III

When the bronchial asthma is aggravated by a cardiac component, the m.b.c. is lower than it is in patients with chronic bronchial asthma and emphysema. In group III, the preliminary determinations of the m.b.c. gave values between 46.2 1/min and 18.21 1/min, or 42.0 per cent and 19.4 per cent of the predicted values. The average of all measurements before drug administration amounts to 29.1 1/min, or 28.1 per cent. Since in this group the average age of the patients is much higher than in group I, only the percentages of the predicted values can be compared. Nevertheless, comparison reveals that in group III the respiratory insufficiency is much more severe.

Changes of the m.b.c. after drug alministration:—In this group of patients, the efficacy of aminophylline and epinephrine is drastically reduced. The average increase produced by aminophylline is only 9.7 1/min, being insignificant in one case. The increase achieved with epinephrine averages 5.8 1/min and was significant in three cases. In three other cases, a small, insignificant increase was observed, while in one patient with most severe respiratory insufficiency, a drop of 1.9 1/min was observed. Sandostene + Calcium produced the greater average increase of the m.b.c., namely, 11.0 1/min and, perhaps most important, the increase was significant in all seven patients, Sandostene without calcium was again relatively ineffective. The m.b.c. had a significant increase in only one patient. The measurements after administration of calcium and saline did not reveal any noticeable change.

Group IV

The average of the m.b.c. determinations before drug administration was 26.9 1/min, or 32.3 per cent of predicted value, clearly lower than the corresponding value of group II. Maximum and minimum values were 38.1 1/min and 17.2 1/min, or 43.8 per cent and 24.0 per cent.

Changes of the m.b.c. after drug administration:—As with groups I and II, the results of groups III and IV closely correspond to each other. In two out of eight cases the increase produced by aminophylline is not significant. Epinephrine failed to increase the m.b.c. significantly in six cases. Sandostene + Calcium increased the m.b.c. in all eight cases to more than 20 per cent of the predetermined value.

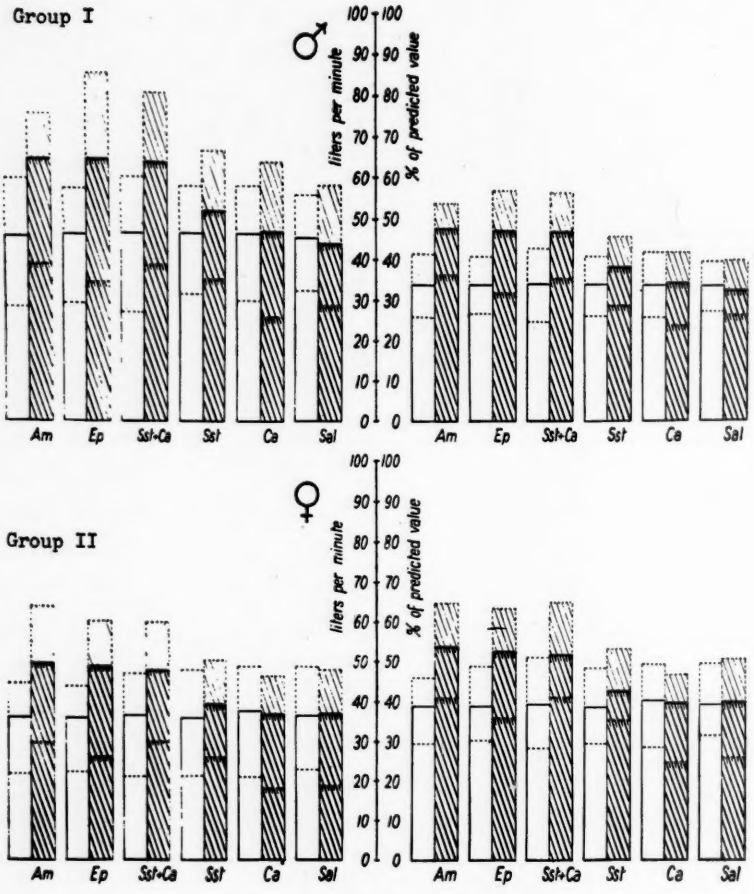

Fig. 1. Changes of the m.b.c. before and after drug administration. Groups I and II. Continuous lines indicate average values, dashed lines, maximum and minimum values.

Total Vital Capacity (t.v.c.)

The t.v.c. shows an unexpectedly close correlation with the m.b.c. Expressed in per cent to the predicted value, the measurements are much higher than those of the corresponding m.b.c., but high values of m.b.c. are always associated with high value of t.v.c. and *vice versa*. Increase and decrease of the m.b.c. usually runs parallel with the corresponding changes of the t.v.c. Only in cases with very low m.b.c. was the t.v.c. reduced to below 50 per cent of the predicted value. The correlation between the m.b.c. and the t.v.c. is shown in Figures 1-4,

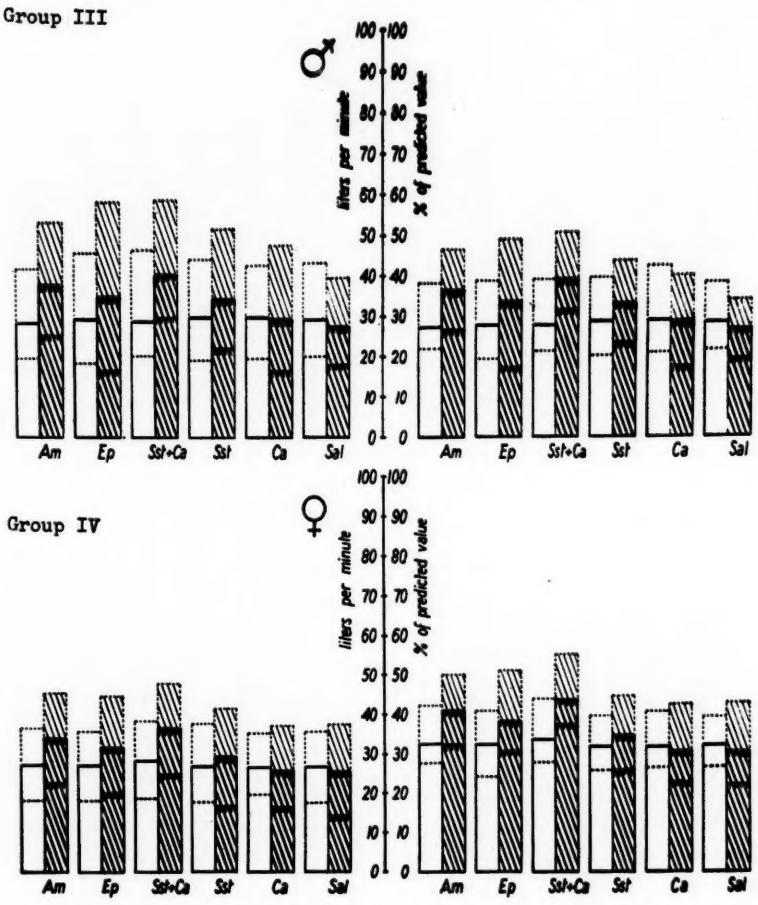

Fig. 2. Changes of the m.b.c. before and after drug administration. Groups III and IV. Continuous lines indicate average values, dashed lines maximum and minimum values.

where the values of these measurements before and after administration of the six test drugs are recorded. The average values are indicated with continuous lines, the maximums and minimums with dashed lines.

Two-Second Vital Capacity (2-sec. v.c.)

The 2-sec. v.c. (the amount of air which the patient is able to exhale in the first two seconds of forced expiration expressed as percentages of his own t.v.c.) showed a good correlation with the m.b.c. only in groups I and II Comparing the value observed in these groups with

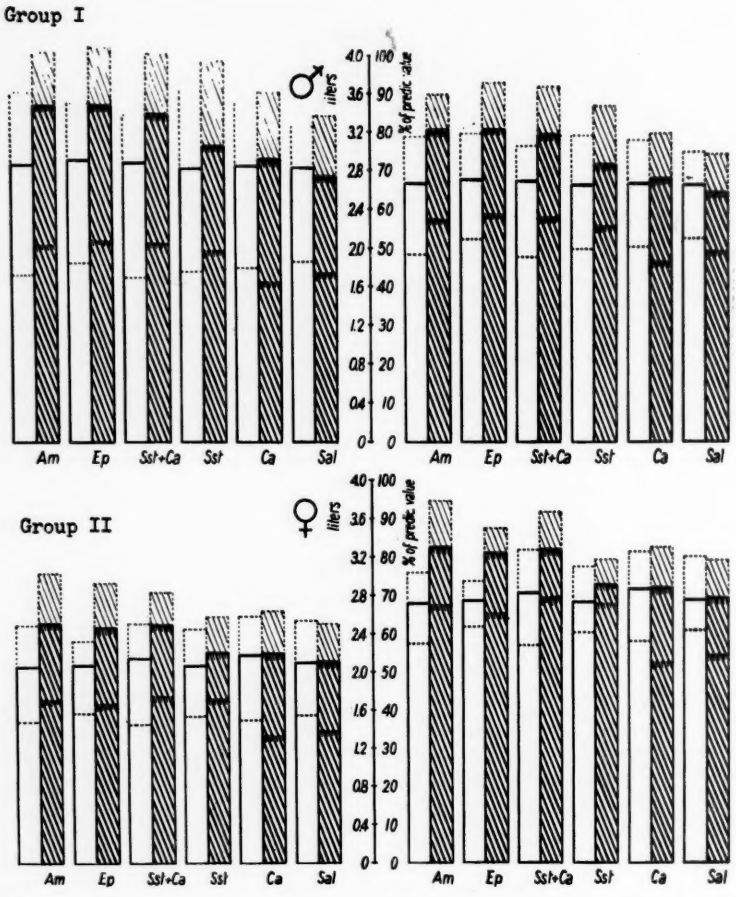

Fig. 3. Changes of the t.v.c. before and after drug administration. Groups I and II. Continuous lines indicate average values, dashed lines maximum and minimum values.

those obtained in groups III and IV, where the patients have a higher average age and more severe dyspnea, a seemingly contradictory increase of the 2-sec.v.c. is observed. A careful check of the values obtained in each individual patient reveals, that when the t.v.c. dropped below 50 per cent of the predicted value, the 2-sec. v.c. shows a tendency to increase. Such patients with most severe dyspnea are not able to maintain the effort of a forced expiration long enough, and therefore after two seconds, they can no longer exhale an appreciable amount of air. Improvement of the dyspnea in these cases can be associated with

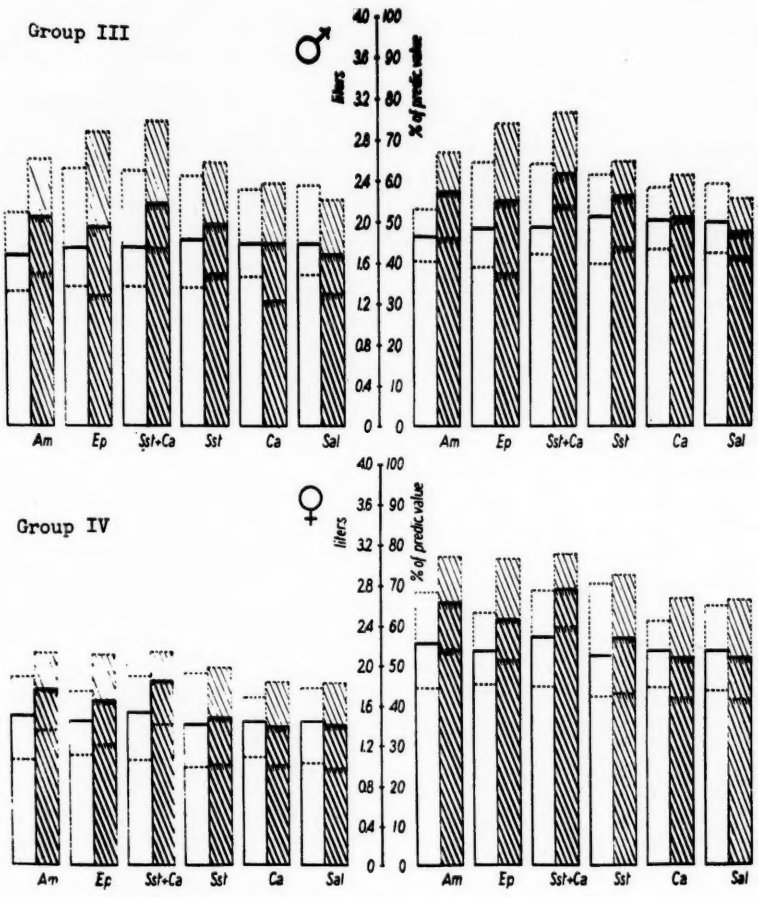

Fig. 4. Changes of the t.v.c. before and after drug administration. Groups III and IV. Continuous lines indicate average values, dashed lines maximum and minimum values.

little or no increase or even a slight decrease in the 2-sec. v.c. The same situation was found by comparing the values of the "air velocity index"

$$\text{AVI} = \frac{\%\text{ of predicted m.b.c.}^{14}}{\%\text{ of predicted t.v.c.}}$$

in the different patient groups. Patients with most severe dyspnea had a small t.v.c. and a corresponding small tidal air volume in performing the m.b.c. Such patients try to compensate their small tidal air volume by an excessively high respiratory rate. The AVI thus shows a ten-

TABLE III. 2-SEC. V.C. AND AVI BEFORE AND AFTER DRUG ADMINISTRATION

	Am		Ep		Sst+Ca		Sst		Ca		Sal	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Group I												
2-sec. v.c.	50.6%	68.3%	49.9%	64.2%	51.0%	64.4%	50.6%	55.6%	50.3%	51.0%	51.1%	50.3%
increase or decrease		+17.7%		+14.3%		+13.4%		+ 5.0%		+ 0.7%		− 0.8%
AVI	0.50	0.59	0.50	0.58	0.51	0.59	0.51	0.53	0.51	0.50	0.50	0.50
increase or decrease		+ 0.09		+ 0.08		+ 0.08		+ 0.02		− 0.01		± 0.00
Group II												
2-sec. v.c.	54.4%	70.0%	55.3%	69.0%	55.7%	67.7%	54.6%	59.4%	56.3%	56.0%	55.1%	54.4%
increase or decrease		+15.6%		+13.7%		+12.0%		+ 4.8%		− 0.3%		− 0.7%
AVI	0.56	0.64	0.56	0.64	0.55	0.63	0.56	0.58	0.55	0.54	0.56	0.56
increase or decrease		+ 0.08		+ 0.08		+ 0.08		+ 0.02		− 0.01		± 0.00
Group III												
2-sec. v.c.	61.4%	68.1%	64.0%	69.3%	61.6%	68.4%	60.1%	61.6%	61.9%	63.1%	61.0%	61.9%
increase or decrease		+ 6.7%		+ 5.3%		+ 6.8%		+ 1.5%		+ 1.2%		+ 0.9%
AVI	0.57	0.62	0.57	0.59	0.57	0.63	0.55	0.58	0.56	0.55	0.56	0.55
increase or decrease		+ 0.05		+ 0.02		+ 0.06		+ 0.03		− 0.01		− 0.01
Group IV												
2-sec. v.c.	61.8%	67.1%	62.3%	65.9%	61.5%	68.5%	62.5%	64.3%	62.3%	61.9%	63.3%	62.6%
increase or decrease		+ 5.3%		+ 3.6%		+ 7.0%		+ 1.8%		− 0.7%		− 0.7%
AVI	0.59	0.62	0.60	0.62	0.59	0.63	0.61	0.61	0.61	0.59	0.60	0.58
increase or decrease		+ 0.03		+ 0.02		+ 0.04		± 0.00		− 0.02		− 0.02

dency to increase. Table III displays the changes of the 2-sec. v.c. and of the AVI before and after the drugs were given.

Respiratory Index (RI)

The RI, (after Gross [17]) failed to demonstrate a close correlation with the other breathing tests. The well-correlated values of the t.v.c. were rendered unreliable by addition of the breath-holding time. The latter value was, in fact, almost independent of the grade of respiratory efficiency. The average values of t.v.c. (expressed in units of 100 cc), of breath-holding time in seconds, and the RI in the four patient groups are compiled in Table IV.

Subjective Impressions and Side Reactions

The patients were directed to note their subjective impressions as they left the hospital (about one hour after drug administration) and for the following twenty-four hours. These feelings were then reviewed at the patient's next appointment. If possible, an attempt was made to discriminate between the changes in the asthmatic condition and side reactions. The subjective impressions concerning the relief of the dyspnea were recorded in four degrees: excellent, good, fair and poor. These subjective reports proved more reliable than expected. They are summarized in Table V.

The side reactions produced by aminophylline were: dizziness (five patients), gastrointestinal disturbances (four), insomnia (six), "nervousness" (three). Epinephrine produced: dryness of throat and tongue (six), anxiety (six), palpitations (seven), and insomnia (three). Sandostene with and without calcium produced: drowsiness (seven), dizziness (two), blurred vision (one), and vomiting (one). In general, the side reactions to Sandostene were far less intense and bothersome. Since Sandostene did not produce any significant change in blood pressure and pulse frequency, it was tolerated better by patients with cardiac disability than were aminophylline or epinephrine.

CONCLUSIONS

1. Sandostene + Calcium is a valuable therapeutic agent in the treatment of chronic asthmatic conditions, whereas the antihistamine without calcium is relatively ineffectual. The enhanced activity of the combination of antihistamine and calcium cannot be ascribed to any additional bronchospasmolytic effect mediated by the calcium, since this agent, when given alone, did not demonstrate such an activity.

2. Though Sandostene + Calcium does not produce such dramatic remissions as can sometimes be achieved with aminophylline and epinephrine injections, it is nevertheless an effective agent. It would appear to be more dependable in patients with bronchial asthma and chronic emphy-

TABLE IV. RI BEFORE AND AFTER DRUG ADMINISTRATION

	Am		Ep		Sst+Ca		Sst		Ca		Sal	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Group I												
t.v.c. in 1/10 l	28.5	34.5	29.1	34.7	28.7	34.0	28.3	30.6	28.4	29.2	28.2	25.7
br.h. time in sec.	25.7	26.0	26.0	25.3	25.3	24.6	23.8	23.7	22.1	21.7	26.2	23.8
"RI"	54.2	60.5	55.1	60.0	54.0	58.6	52.1	54.3	50.5	50.9	54.4	51.3
Group II												
t.c. in 1/10 l	20.7	25.1	20.7	24.7	21.6	24.9	20.7	22.0	21.9	22.0	20.7	21.1
br.h. time in sec.	18.9	18.9	14.3	17.3	18.1	17.4	18.0	18.7	18.4	20.0	19.3	20.0
"RI"	39.6	44.0	35.0	42.0	39.7	42.3	38.7	40.7	40.3	42.0	40.0	41.1
Group III												
t.v.c. in 1/10 l	16.7	20.6	17.7	19.7	17.6	21.9	18.4	19.9	18.0	18.0	17.9	16.9
br.h. time in sec.	18.3	16.0	18.4	17.2	17.5	17.4	17.2	15.8	16.4	15.3	17.2	15.0
"RI"	35.0	36.6	36.1	36.9	35.1	39.3	35.6	35.7	34.4	33.3	35.1	31.9
Group IV												
t.v.c. in 1/10 l	14.8	17.4	14.4	16.5	15.3	18.4	13.9	15.2	14.4	13.9	14.3	13.9
br.h. time in sec.	15.1	12.4	12.4	14.0	12.7	14.6	15.0	13.3	12.0	14.2	12.2	14.2
"RI"	29.9	29.8	26.8	30.5	28.0	33.0	28.9	28.5	26.4	28.1	26.5	28.1

TABLE V. SUBJECTIVE CHANGES OF DYSPNEA AFTER DRUG ADMINISTRATION

	Am				Ep				Sst+Ca				Sst				Ca				Sal			
	Groups				Groups				Groups				Groups				Groups				Groups			
	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
E	5	3	1	1	3	2	0	0	4	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
G	5	3	2	2	5	2	3	1	4	5	5	4	0	1	1	1	2	1	1	0	1	1	0	1
F	2	1	2	3	2	2	1	3	3	2	2	3	5	2	3	2	2	1	1	1	2	1	1	1
P	0	0	2	2	2	1	3	4	1	0	0	1	6	4	3	5	8	5	5	7	9	5	6	6

E—excellent G—good F—fair P—poor

sema, for it failed to produce a significant increase of the maximum breathing capacity in only one of the thirty-four patients, whereas aminophylline failed in three cases and epinephrine in fourteen. The subjective impressions of the patients support these findings, viz., two patients reporting poor results after Sandostene + Calcium, four after aminophylline and ten after epinephrine. The comparison becomes even more advantageous for the combined preparation if only the patients with cardiac dysfunction are taken into consideration.

3. Sandostene, with and without calcium, was generally better tolerated than the control drugs. One patient complained of nausea and vomiting, one of dizziness and blurred vision and three of heavy drowsiness. These were the only troublesome side effects. Four more patients reported a mild sedative effect and one a passing dizziness. The latter side effects evidently did not concern the patient and were elicited only on questioning.

4. The following observations concerning the respiratory function tests merit consideration.

(a) The total vital capacity shows a better correlation to the maximum breathing capacity than is generally assumed.

(b) When the total vital capacity is reduced to below 50 per cent of predicted value the two-second vital capacity shows a seemingly contradictory tendency towards increase in most severe asthmatic conditions.

(c) The "Air Velocity Index"

$$\text{AVI} = \frac{\%\text{ of maximum breathing capacity}}{\%\text{ of total vital capacity}}$$

provides the best correlation with the 2-second vital capacity in all groups.

(d) The "Respiratory Index" (RI = t.v.c. expressed in units of 100 cc + breath-holding time in seconds) failed to prove its accuracy as a ventilatory function test in this study.

SUMMARY

1. Sandostene + Calcium is an effective and well-tolerated agent in the therapy of chronic bronchial asthma. The best results were achieved in elderly patients presenting a concomitant cardiac dysfunction aggravating their respiratory condition.

2. Three weekly injections of 10 cc each of Sandostene + Calcium were generally sufficient to maintain the improved status of these patients and constituted a practical form of treatment. Where necessary, injections may be given more frequently and are well-tolerated over long periods.

3. Five respiratory function tests, a new one among them, were employed and an analysis of their usefulness as objective determinants is presented.

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A NEW NON-NARCOTIC, ANTITUSSIVE DRUG

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THE COUGH reflex is acted upon by antitussive agents at two points in particular, centrally in the medulla oblongata, and peripherally in the afferent and efferent branches of the reflex arc. Relief of cough by a peripheral point of attack is possible by local anesthesia. In bronchoscopy, as done in Europe, local anesthetics are used (1) by instilling novocaine or procaine into the pleural space, or (2) by subpleural infiltration with the same drug. In this country, bronchoscopy is done by a local application of an anesthetizing drug to the nasopharynx and trachea. However, the use of local anesthetics as antitussive agents is impossible in those cases where the receptors of cough stimuli cannot be reached locally.[2,4]

Antitussive agents with central action have long been known. Narcotics are a good example. However, they have many disadvantages such as a depressing action on respiration, nausea, constipation, sedation, and the possibility of addiction.[2,4]

A desirable antitussive would be one which, in addition to avoiding the undesirable side effects of the narcotics, would not thicken the sputum nor interfere with the patient's ability to raise this natural sputum. Ideally, the antitussive agent should not produce tolerance or sensitivity.

A search for a substance having a selective anesthetizing action on the dilatation receptors of the lung was motivated by the knowledge that during a fit of coughing the air is not only expelled forcibly, but also drawn in forcibly. The latter phenomenon is party ascribed to the increased volume of inspiration necessary for the cough. A close study of this relationship has shown that there is a striking parallelism between the intensity of the cough and the depth of the inspiration which immediately precedes it. An explanation may be that the respiratory center receives more and more intensified expiratory impulses reflexly when there is an increase in depth of inspiration (Hering-Breuer reflex). These expiration impulses in question, which are transmitted along the vagus nerve, come from the dilatation receptors located in the lung.[2,4,6]

In animal experiments, it was noted that fits of coughing cease if one can arrest the dilatation of the lung during inhalation. This was achieved during the experiment by closing the respiratory tract just before the beginning of inspiration, in the pause following expiration, by immediately opening a canula which had previously been introduced into the pleura.

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The thorax can thus normally move in inspiration without dilatation of the lung.[1]

From the preceding one may assume that the increase in the sensitivity of the dilatation receptors during inspiration is an important part of the mechanism of coughing. It this assumption is correct, it could be possible to arrest cough by anesthetizing the dilatation receptors. A dilatation receptor anesthetic would, therefore, be an antitussive agent which, in contrast to the well-known cough remedies such as morphine, codeine, et cetera, would not intervene centrally, but rather peripherally in the reflex mechanism of the cough. An anesthetic with a selective action on the dilatation receptors of the lung would possess a high degree of clinical tolerability without the disagreeable central side effects of narcotics or the autonomic effects on circulation produced by local anesthetics.[2,4]

In animal experiments, it was noted that analogues of local anesthetic drugs used in surgery had greater dilatation receptor anesthetic action than the original drugs. Of these Tessalon®* proved to be the most effective. It is a polyglycol, alkaloid-free, antitussive agent with the following chemical formula: methoxypoly(ethyleneoxy)-ethyl-p-butylaminobenzoate; the structure formula is:

(n) signifies principle component is 9 with adjacent homologues.

Large-scale clinical trials in Europe extending over more than two years and involving over 2,000 cases have shown this new drug to be effective clinically and in many respects superior to narcotics. It was well tolerated by all patients with no effect on circulation, blood count, or urine. There were no reports of sedation, habituation, euphoria, or inhibition of the respiratory center.[1-6]

METHOD

Fifty unselected patients with diagnoses of chronic bronchitis and pulmonary emphysema, who had been under stabilized treatment in the allergy clinic for at least one year, were given 50 mg Tessalon capsules to be taken with bronchodilator cough mixtures from which narcotics (codeine or Hycodan®) were now omitted. At the beginning, one capsule and later two capsules (100 mg) were used. Medication was given three or four times daily with additional doses, if necessary. In every patient, it was also tried without the bronchodilator cough mixture to

*Tessalon® was supplied through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

determine the effectiveness of the new drug by itself. Patients were seen at least once a week and blood counts and urinalyses were performed before, during and after antitussive therapy.

THE PATIENTS

The patients ranged from thirty-five to seventy-six years of age, the average being fifty-nine years. The mean duration of chronic lung disease was eighteen and a half years. Practically all patients had a chronic cough productive of one-quarter to one cup of thick, gray sputum every twenty-four hours. The productive cough relieved totally or in part the shortness of breath and wheezing in all these patients. No seasonal or geographical influences were noted, but symptoms were aggravated by damp weather or acute upper-respiratory infection. The cough and wheezing, while annoying during the night, were much worse on first arising in the morning. There was no instances of definite allergy. All had received iodides, xanthines, and various bronchodilator drugs as well as injections of stock vaccines.

RESULTS

The fifty patients included in the study were under treatment with the new drug from eight to sixty-nine days, averaging forty-five days per patient, for a total of 2,288 patient-days.

Evaluation was of necessity largely subjective, although in many cases the patient's roommates corroborated his story. Four patients were eliminated from the study group due to unreliability, alcoholism, mental defect or lack of cooperation. Others, while claiming no change in cough, insisted on continuing the new medication.

Classification of response was as follows: Excellent (75 to 100 per cent relief of cough), good (50 to 75 per cent relief), fair (25 to 50 per cent relief), and none (0-25 per cent relief). Three patients who claimed no relief but insisted on continuing the antitussive agent are classified under "Fair."

In approximately 70 per cent of patients, it was found that 100 mg gave much greater relief than did 50 mg, particularly when taken on retiring and either before or on arising. In some instances, 100 mg three or four times a day seemed to afford maximum relief; however, at times 50 mg at the same intervals or as needed was as effective as the larger dose.

Doses were individualized for each patient starting with 50 mg until maximum relief was attained. The results were as follows:

Relief of Cough	*No. of Patients*	*Per Cent*
Excellent	26	52
Good	14	28
Fair	7	14
None	3	6

The following was observed as to the effect of this antitussive on sputum: thirty-two patients showed less sputum, two showed more,* and sixteen produced the same amount. In three patients the sputum was heavier, in twenty-seven it was lighter, and in twenty there was no change in the consistency.

Patients noted that the new capsules taken without the bronchodilator mixture stopped cough as well, but exhibited no bronchodilating effect.

There were no sight reactions of toxicity noted in the dosage used, and blood counts and urinalyses showed no change.

DISCUSSION

Although all of these patients complained of wheezing and shortness of breath, neither one of these symptoms became worse when cough was lessened by Tessalon. This may be attributed to easier production of thinner sputum without paroxysms of coughing. Blackouts, weakness and vomiting which had been present in many patients prior to the use of the new antitussive agent, were also inhibited, possibly due to the prevention of severe cough with retching and cerebral anoxia.

This drug was noted to act in fifteen to twenty minutes regardless of dosage and to be effective from three to eight hours. However, some patients noted that it did not become effective until they had taken 200 to 300 mg daily for three to seven days. Two out of three patients noted lessened sputum, and more than half that the sputum became lighter in consistency. The only two patients who had more sputum found it easier to produce due to thinning.

There is apparently some cumulative action, as several patients remarked that it seemed more effective from the second week on, than during the first week of therapy.

Unfortunately, it is of little if any value in acute bronchitis, possibly due to the lack of influence on the co-existing acute tracheitis which probably instigates the cough.

SUMMARY AND CONCLUSIONS

Fifty patients who had suffered from asthmatic bronchitis and pulmonary emphysema for many years were given Tessalon capsules. This new non-narcotic, antitussive agent gave better results in 100 mg dosage, which was effective from three to eight hours. Apparently the most important actions were greatly reduced cough and reduction in consistency and amount of sputum. No toxicity or side reactions of any kind were noted. Eighty per cent of those treated noted good or excellent relief of cough.

*These patients noted more but lighter sputum.

ACKNOWLEDGMENT

The author wishes to express his appreciation for the assistance of Robert R. Smith, M.D., and Freeland G. White, B.A., in the preparation of this paper.

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Brown General Hospital
Veteran's Administration

Submitted November 14, 1956

ATOMIC ENERGY AND THE LIFE SCIENCES

Perhaps the kernel of the situation lies in the fact that the greater man's knowledge of the laws of nature, the more substances he can create that have never actually been found in nature. We can thus not only make completely unfamiliar substances but also release forces that in quality or intensity are not to be found in the natural world. Virtually a second world for study and exploration comes thus into being as a result of profoundly understanding the laws that govern the phenomena of the world about us—the first world we studied and explored. Nor is this the end of the possibilities before us. There is almost an infinity of possible applications of new substances and new forces. Indeed, the case for finding the uses of new substances for human needs, the harnessing of new forms of energy to serve human purposes, rest in the phrase of Protagoras the Sophist; *homo mensura*—"man is the measure of all things." And what is to measure the needs and purposes of man?—ALAN GREGG, Report of the United States Atomic Energy Commission, July, 1949.

A NEW FORMULA FOR RELIEF OF ASTHMATIC ATTACKS

K. A. BAIRD, M.A., M.D., F.A.C.A.
Lancaster, New Brunswick

The tendency of ephedrine to stimulate or excite is neutralized, at least partially, by the use of some barbiturate in various tablets and capsules popularly prescribed to relieve asthmatic attacks.

The writer combined the sedative antihistamine Phenergan®* with ephedrine, and results seem to justify making this preliminary report. In theory, such a combination might not only avoid barbiturate medication but add certain antiasthmatic properties of this antihistamine, whose makers suggest that there is a certain amount of anticholinergic action, as well as sedative and antihistaminic effects. Adult patients were given 25 mg each of ephedrine and Phenergan for a dose.

Dr. R. F. Hughes of Hamilton made a "blind test" of this formula for the writer on five cases of asthma, and reports his impression that it is "equal to the other forms of antiasthmatic tablets."

The writer treated twenty-three asthmatic patients, all of whom obtained relief of attacks. Four preferred some other formula, five preferred the new formula to previous medication, and fourteen were satisfied and did not wish to try anything else.

Six cases of attacks of headache or dizziness, which seemed associated primarily with allergic sinus congestion, all obtained relief.

Eight of the twenty-nine cases noticed some sedative effect. After taking the formula a number of times, five said this was much less and not important. One reserved it for his preferred treatment when needed *at night,* and the other two were among the four who preferred other formulae.

The writer considers this formula worthy of further investigation on larger numbers of patients by other allergists. This can easily be done by prescribing an equal number of tablets of Phenergan (25 mg) and capsules of ephedrine hydrochloride (3/8 gr-25 mg) with directions to take one tablet and one capsule for a dose.

562 Dunn Avenue

Submitted March 13, 1957
Resubmitted April 19, 1957

Phenergan used in these tests was kindly supplied by Poulenc Limited, Montreal, Canada.

ANTIGENIC ANALYSIS BY GEL DIFFUSION

III. Pollens of the Amaranth-Chenopod Group

ROGER P. WODEHOUSE, Ph.D.
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THE Amaranthaceae and Chenopodiaceae comprise a number of hay fever plants such as carelessweed, Western waterhemp, Russian thistle and shadscale which are particularly troublesome in the arid regions of western United States. They are members of the natural order Chenopodiales and botanically very closely related to each other. They are sharply set off from the many other families of the order by being all primarily wind pollinated which, together with their weedy habits, is chiefly why they happen to cause hay fever.

It has long been known that the pollens of the various species of these two families cross-react to a large extent, showing a high degree of antigenic similarity both within the family and across the family boundaries.[1,3] Hay fever patients who are sensitive to the pollen of one species are always sensitive to others of this group. Lamson[1] found that of patients reacting to pigweed, 79 per cent reacted also to Russian thistle and others, and states, "It is suggested that the pollen extract of each species contains many minor antigenic properties typical of the great majority of other species even though they may be members of different genera. These findings apparently lend support to the botanic classification and indicate a method of studying biological relationships."

There is good reason to believe that if these relationships were better understood the task of diagnosing and treating this type of hay fever could be simplified. This is also true of the preparation of the appropriate extracts, since the pollens of some species are not readily available owing to difficulty of collection, whereas others are easily obtained. As a rule, the ease of collection and clinical importance of a pollen go hand in hand, because both depend to a large extent upon the pollen's abundance.

The gel diffusion techniques have been found to be well adapted to revealing the antigenic patterns of pollen extracts in a way to manifest their similarities and differences.[4,5]

MATERIALS AND METHODS

Antigens.—

Amaranthaceae

Carelessweed, *Amaranthus palmeri* Wats., Cwd.*

Dr. Wodehouse is Associate Director, Research in Allergy, Lederle Laboratories Division, American Cyanamid Co., Pearl River, New York. He is an Associate Fellow of The American College of Allergists.

*Each antigen and antiserum is followed by its abbreviation used in the figures.

Pigweed, *A. retroflexus* L., Pwd.
Spiny Amaranth, *A. spinosus* L., Sam.
Western waterhemp, *Acnida tamariscina,* Wood., Whp.
Chenopodiaceae
Russian thistle, *Salsola pestifer* A. Nels., Rth.
Burning bush, *Kochia scoparia* Roth, Bbu.
Lambsquarters, *Chenopodium album* L., Laq.
Shadscale, *Atriplex canescens* Nutt., Ssc.
Annual saltbush, *A. wrightii* Wats., Sbu.
Unrelated Controls
Ragweed *Ambrosia elatior* L., Rwd.
Timothy *Phleum pratense* L., Tim.

Antisera.—

Anti-carelessweed, P41.
Anti-Russian thistle, P51.

The pollen extracts that were used for the tests were prepared, 1:20, W/V, in Coca's solution, sterilized by filtration and preserved with 1:5000 Merthiolate, except that of carelessweed. This was reconstituted from lyophilized material which had been prepared in the same way, then dialysed fifteen hours in running tap water. It has already been shown that dialysis and lyophilizing have no effect upon the antigenicity of pollen extracts, except a slight loss of potency from dialysis.[6]

The pollens from which the extracts were made were all visually nearly or quite pure, always with much less than one per cent contamination with other pollens. All were obtained from T. R. Stemen Laboratories, except burning bush and shadscale which were obtained from pollen collector Hafford.

The two antisera were prepared as previously described.[4] The carelessweed extract used for injecting the rabbits was the same as above. The Russian thistle extract, however, was prepared from pooled pollen from various sources and, while nearly pure, except for some sand and plant fragments, showed contamination with ragweed, grass and sagebrush pollen totaling less than one in 300.

The Ouchterlony[2] double diffusion technique was used with the reactants diffusing from penicillin assay cups, generally three, standing on the surface of agar at 20 mm intervals in the triangular arrangement. Extracts undergoing comparison were placed in two of the cups and one or the other of the antisera in the third. Each precipitation band that is formed is considered to represent one or more antigen-antibody reactions. Antigens that are alike or similar precipitate in bands that interfere with each other, tending to join and form arches about the serum source. Those that are different cross without interference. Ordinarily, however, if completely different, the heterologous antigen fails

to form any precipitation bands since it finds no homologous antibodies. Only if the two antisera are combined do two sets of well developed bands form, in which case they cross without interference, in the pattern of nonidentity.

EXPERIMENTAL STUDIES

An extract of carelessweed was compared with those of ragweed and timothy diffusing against anti-carelessweed serum, P.41 (Figs. 1, 2). The same was done with Russian thistle diffusing against anti-Russian thistle serum, P.51 (Figs. 3, 4) to see what totally unrelated pollens will do. Carelessweed and Russian thistle form their typical patterns with no interference from the heterologous pollens, the pattern of complete nonidentity.

The pattern of carelessweed (Fig. 1) is seen to consist of two small bands forming close to the serum source. These have a compact translucent appearance and a bluish color and are generally referred to as the inner blue bands. These are followed by the major band which is white, opaque and, in this case, obviously double, though this is not always apparent. This is followed by a sharp but less dense band. Next comes a fine sharp band, followed by one that is fine and diaphanous then two that are heavier, very close together and sometimes superimposed. Beyond these comes a rather broad nebulous band which appears only late in the development of the pattern, a total of nine bands.

The Russian thistle pattern is similar but the two inner blue bands are either superimposed or very close together. Between them and the major band are two that are weak. The major is double, as with carelessweed, but more opaque and longer. This is followed by four or five more bands of varying intensity making a total of nine or ten.

Though the timothy and ragweed pollens have no effect on the carelessweed or Russian thistle patterns, each forms two or three independent bands of its own, very faint but unmistakable. In attempting to discover the origin and significance of these, the carelessweed and Russian thistle antisera were tested with sagebrush, Bermuda grass, mountain cedar, elm, house dust, various bacteria, Strepomycetes and other antigenic materials. Of these, only Bermuda grass and sagebrush gave similar precipitation bands, suggesting that the two antisera may contain traces of grass, ragweed and sagebrush antibody, possibly due to contamination of the pollen used for injecting the rabbits, because these are the only species among those tested which grow in the region where the immunizing pollens were collected. If this is the explanation, then these contaminating pollens are capable of functioning in extraordinarily minute quantity to engender antibodies, much less than is required to visibly react with their antibodies, for the bands cross those of the homologous antigens without any noticeable interference from the latter.

Two extracts of Russian thistle pollen, made from different batches,

were tested diffusing against P.51 serum (Fig. 5). All bands interfere and form nearly completely symmetrical arches, showing the pattern of complete identity.

Assuming that the taxonomy of the Chenopodiales truly reflects the phylogeny of the group, three sets of comparisons were made: (1) between the members of the Amaranthaceae, (2) between those of the Chenopodiaceae, and (3) between those of the two groups across the interfamily boundary. For the most part, those of the Amaranthaceae were diffused against antiserum P.41, which should detect in them all the antigens belonging to carelessweed; and those of the Chenopodiaceae were diffused against antiserum P.51, which should detect all the antigens belonging to Russian thistle. Comparisons between the members of the two families were done against both antisera.

THE AMARANTH GROUP

Carelessweed was compared with pigweed (Fig. 6). The pattern forms with all bands fusing and forming arches over the serum source, showing that all the antigens of carelessweed are present in pigweed and in very nearly the same proportion, except those represented by the two outer bands of each, showing that their antigens occur in different proportions.

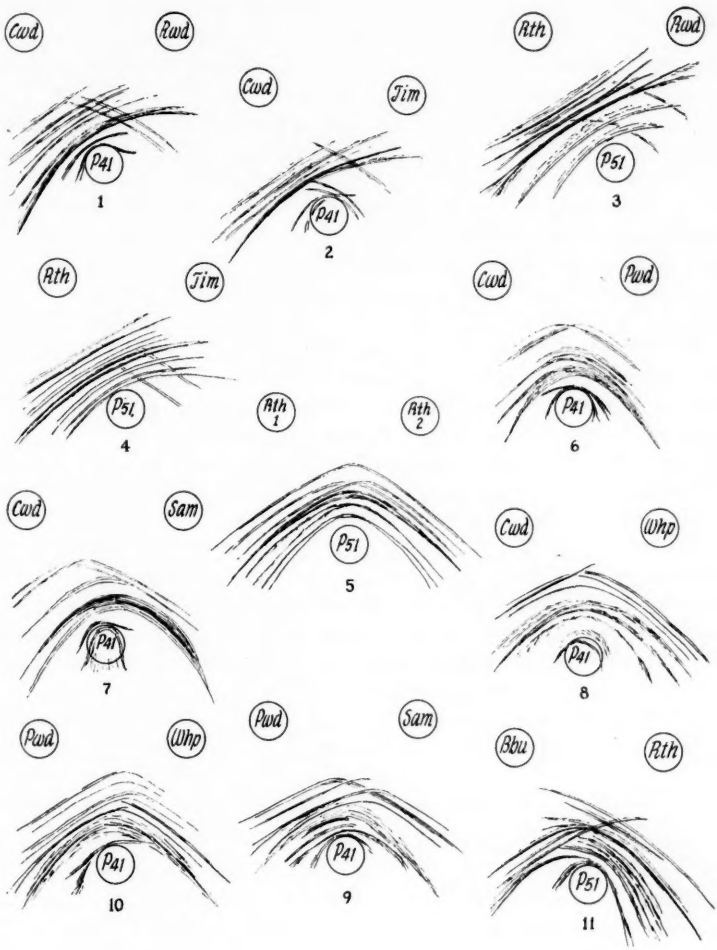
Carelessweed was also compared with spiny amaranth (Fig. 7) with similar results, except that in this case one of the blue bands near the serum source is not represented in the latter pollen. When compared with western waterhemp (Fig. 8) an even closer agreement was found; all bands, except one, fuse and form nearly symmetrical arches, despite the fact that waterhemp is considered to belong to a different genus.

Similarly, pigweed was compared with spiny amaranth (Fig. 9), and with waterhemp (Fig. 10). Both showed almost complete identity, except for part of the inner blue band which appears to be somewhat deficient in the pollens of the two latter species. The extract of the waterhemp pollen is obviously weaker than that of the pigweed, but no antigens are entirely lacking.

It is thus seen that pigweed, spiny amaranth and waterhemp contain antigens identical with those of carelessweed and with each other, but in slightly different proportions. The only antigens which may be lacking in any is that represented by part of the small inner blue band in spiny amaranth and that represented by one of the small outer bands in western waterhemp.

THE CHENOPOD GROUP

When Russian thistle was compared with burning bush diffusing against anti-Russian thistle serum (Fig. 11), they gave the pattern of partial identity. The inner blue and major bands are common. The outer blue bands of each are similar but they do not join. The other bands of the



Figs. 1-11

EXPLANATION OF FIGURES

All figures were drawn free-hand from agar diffusion plates about two weeks old, and are reproduced at a reduction of 0.5. The circles represent penicillin assay cups. In all cases, except Figs. 23 and 28, three were used in triangular arrangement. Figure 23 represents the pattern of four cups of a 7-place hexagonal arrangement, the others omitted because they were irrelevant to the present discussion. Figure 28 represents a five-place square arrangement. For further description see text.

Russian thistle pattern, except one, are all bent more or less. Thus, all the antigens of Russian thistle except one are represented in burning bush to at least some degree. This is the closest relationship found between any two members of this group.

Russian thistle and burning bush were also compared diffusing against anti-carelessweed serum. Four weakly-developed bands were formed, apparently not including the major but including the inner blue bands, all in the pattern of complete identity. This shows that four of the antigens which are common to Russian thistle and burning bush are the same antigens which they share with carelessweed. This is confirmed in the comparison of Russian thistle and carelessweed (Figs. 16, 17) diffusing against P.41 and P.51.

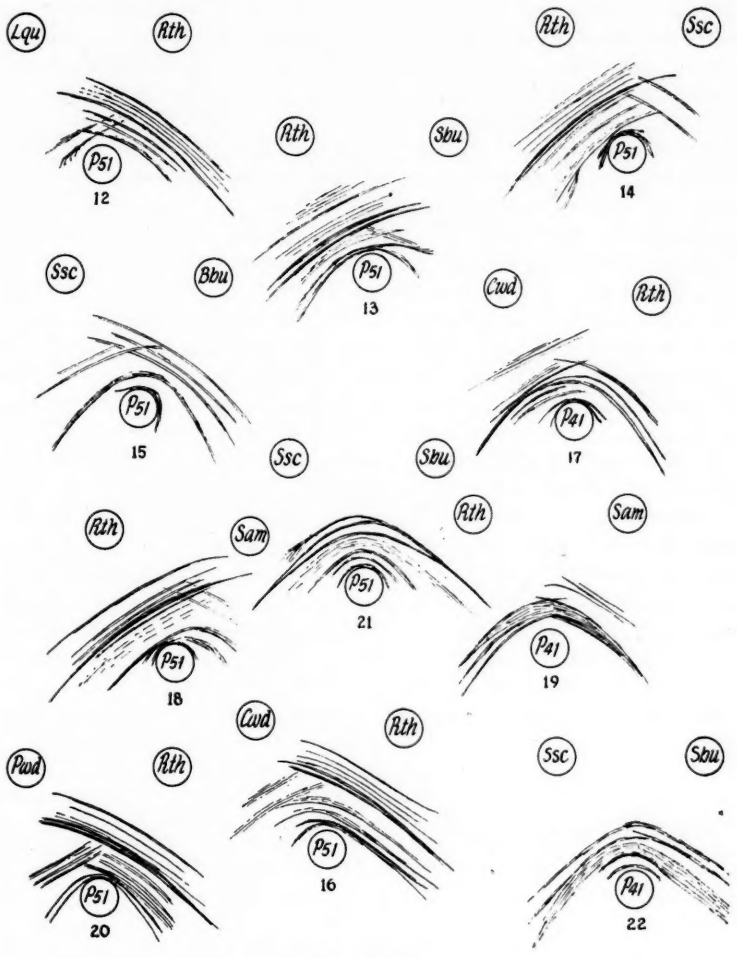
When Russian thistle was compared with lambsquarters (Fig. 12), it gave the pattern of almost complete nonidentity, except for a slight bending of the homologous bands. Also lambsquarters forms two independent bands of its own. Russian thistle compared with annual salt bush (Fig. 13); only the inner blue band was shown to be in common. Otherwise, the homologous pattern is undisturbed, but the salt bush makes a single faint independent band of its own. Russian thistle compared with shadscale (Fig. 14) showed only the inner blue band to be common. Except for a slight turning of the ends of some of the inner group of bands, the homologous pattern was undisturbed, but shadscale makes two independent bands of its own. When shadscale was compared with burning bush diffusing against P.51 (Fig. 15), only the outer blue band is shown to be common to the two.

It is thus seen that there is much less similarity between the members of the Chenopod group than between those of the amaranth group.

INTERGROUP COMPARISONS

Russian thistle compared with carelessweed diffusing against anti-Russian thistle serum, P.51 (Fig. 16), showed only the inner blue band completely in common, but carelessweed sharply bends three others of the homologous pattern, showing that the same or similar antigens are present in carelessweed but in smaller amount. Carelessweed also makes two independent bands with the anti-Russian thistle serum. When these same two extracts were compared diffusing against carelessweed serum, P.41 (Fig. 17) the same four bands of the Russian thistle that were common or bent before now form complete arches. Thus Russian thistle and carelessweed have at least four antigens in common. Also each has five antigens only slightly or not at all represented in the other.

Russian thistle compared with spiny amaranth, diffusing against P.51 (Fig. 18) has the three inner bands in common, and spiny amaranth makes two independent bands with the heterologous serum. Diffusing against P.41 (Fig. 19), the same three bands are in common but spiny amaranth makes three that are not.



Figs. 12-22.

Similar patterns were obtained when pigweed and waterhemp were compared with Russian thistle (Figs. 20, 23). These have only two or three inner bands in common with Russian thistle, and the latter has six or more which are not represented in pigweed and waterhemp.

When burning bush is compared with pigweed diffusing against P.41 and P.51 (Figs. 24, 25), three of the inner group of bands and one of the outer are in common, but each has at least two antigens which are not represented in the other.

Burning bush compared with spiny amaranth diffusing against P.41

(Fig. 26) shows five bands in common, but spiny amaranth has three that are lacking in burning bush. Diffusing against P.51 (Fig. 27) burning bush makes only four bands, all of which are decidedly bent by spiny amaranth, showing the presence of the antigens represented by these to a lesser degree in the latter.

When burning bush is compared with carelessweed diffusing against P.41 (Fig. 28), it shows three bands in common and one independent, while carelessweed makes seven or more that are not common. When compared with waterhemp diffusing against P.51, it shows no bands in common but waterhemp makes two that are independent (Fig. 29).

Lambsquarters compared with pigweed diffusing against P.41 (Fig. 30) shows three or more bands in common and one independent, but the outer bands of the amaranth pattern are undisturbed.

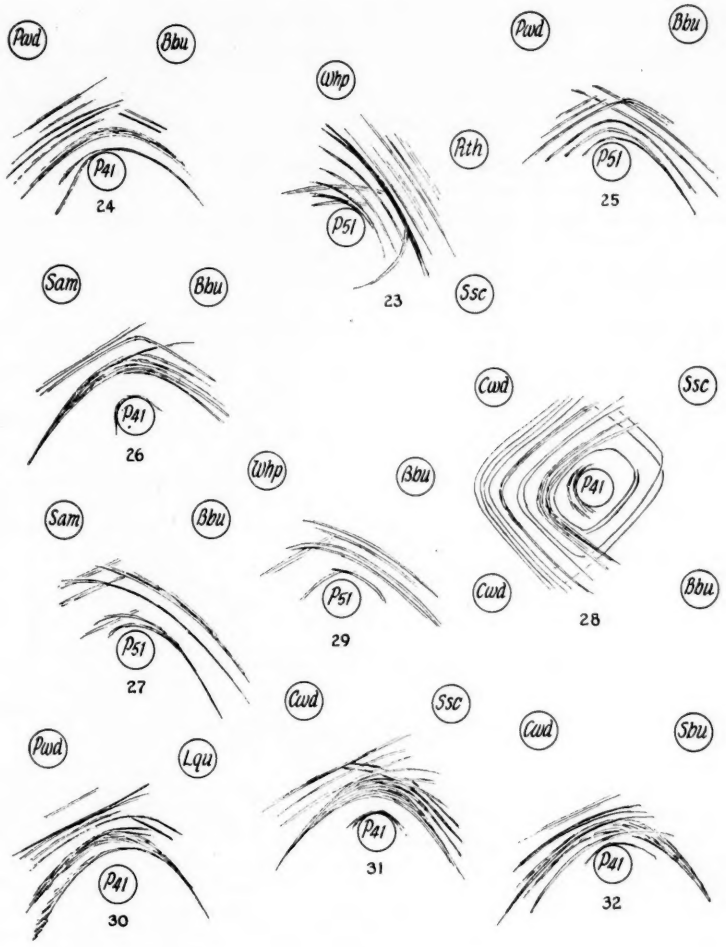
Shadscale compared with carelessweed diffusing against P.41 (Fig. 31) shows five or six bands in common, whereas, compared with Russian thistle, diffusing against P.51 (Fig. 14), it has only the inner blue band in common and makes two independent bands. Thus it has more antigens in common with carelessweed than with Russian thistle.

Annual salt bush compared with carelessweed diffusing against P.41 shows only one band completely in common and a marked bending of the four inner bands (Fig. 32). When shadscale and annual salt bush are compared diffusing against P.51 and P.41 (Figs. 21, 22), patterns of almost complete identity are obtained in both cases. In one six and in the other five bands are formed, all except a part of one in common (Fig. 22) showing that insofar as their patterns are expressed they are antigenically nearly identical. However, since neither species is homologous with either antiserum, the patterns are probably incomplete; the missing bands if present might prove either identity or nonidentity. In any event, it is certain that at least the majority of their antigens are common to the two species, which is in agreement with their botanical classification.

SUMMARY

Pollen extracts of four common hay fever plants of the Amaranthaceae were compared with each other diffusing against anti-carelessweed rabbit serum. It was found that they all contained the same antigens in nearly the same proportions.

Similar tests with five common hay fever pollens of the Chenopodiaceae, using Russian thistle antiserum as the antibody source, showed much less similarity. None has the same precipitation pattern as Russian thistle. Burning bush is the closest. It has four of its antigens in common with Russian thistle and its bending effect on all the bands of the Russian thistle pattern indicates that it has at least some of the same or similar corresponding antigens. The four completely common antigens appear to be also common to the members of the Amaranthaceae. Much



Figs. 23-32

less agreement is found among the other species of the Chenopodiales; in some cases little or none was found.

This is considered evidence that, in the diagnosis and treatment of hay fever from the anemophilous chenopodiales, the pollen of any one member of the Amaranthaceae will serve for the other members of that family, but will furnish only partial coverage for some of the Chenopodiaceae which is an antigenically heterogeneous group and cannot be wholly represented by any one species.

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Lederle Laboratories

Submitted February 19, 1957

HISTORICAL CASE REPORT

I can report a similar condition: It occurred to a young lady, very intelligent and free from feelings of social insecurity and fear, who for many years enjoyed undisturbed health. Once while away from home, she felt quite comfortable until she had to sleep in a bed made predominantly of eiderdown. She spent a sleepless night, tortured by a strange restlessness and irritation, the cause of which she felt unable to determine. In the morning she complained of a heaviness and emptiness of the head, but not of headaches, assuming this condition to be due to the unusual sleeplessness. She remained this way until after lunch. Overpowered by tiredness and without bias against the resting place of the previous night, she decided to rest in the same bed. Experiencing the same discomfort in an increasing way, she feared the start of an illness. This she attributed to the difficult journey, until she examined the bed and found its fillings consisted of eiderdown. Then she suddenly remembered that this material had always caused her similar troubles.—Georg Ernest Stahl (1660-1734), *Disquisition de Mechanismi et Organismi Diversitate,* 1706. (Submitted by Dr. Ernest Harms)

Progress in Allergy

BRONCHIAL ASTHMA VI

Critical Review of Literature

LEON UNGER, M.D., F.A.C.A., and JAMES H. JOHNSON, A.C.A. (Assoc.)
Chicago, Illinois

(Continued from July-August issue)

ASTHMA IN CHILDREN

Asthma in infancy and childhood continues to draw discussion. In addition to Glaser's excellent monograph on the subject,[17] a large number of articles have appeared from various parts of the world. Most of these are very good and they cover etiology, diagnosis, prognosis and therapy. Many papers cover all of these.

Bentolila,[243] from Rosario, Argentina, studied 330 asthmatic children. The allergic cause was found in 80 per cent; 60 per cent were boys; the attacks were especially frequent between the ages of three and ten. Upper respiratory infections were outstanding causes, followed in order by inhalants, foods, molds and pollen. Emphysema was the most common complication, followed by bronchiectasis and atelectasis. Jensen[244] also believes bacterial infection of great importance; it seemed to him to be the sole releasing factor in about 33 per cent of his 600 children (62 per cent boys, 38 per cent girls); in another 40 per cent infection was a complicating factor. House dust, feathers, molds and grass were also important.

The relation between "eczema" in children and asthma has been discussed. Vowles et al,[245] in seventy-eight children, report that the eczema cleared up in one-fourth by the age of three, but was still present in the rest at thirteen. Asthma, recurrent bronchitis or seasonal rhinorrhea occurred in 73 per cent, as compared to only 5 to 7 per cent of a control group of fifty-seven children. Fifty per cent had asthma alone, as compared with 2 per cent in the control group. One or more attacks of pneumonia had occurred in 22 per cent of the patients, but in only 2 per cent of the control group. [This high incidence of "pneumonia" suggests that it was really only another evidence of impending bronchial asthma. The two are often confused in children.] Lobitz and Dobson, dermatologists, reiterate the fact that eczema in childhood is frequently followed by asthma.[246]

Asthma is a common disease in Scandinavia, reports Walther.[247] The general allergic predisposition, not a special form of allergy, is hereditary. Eczema in infancy and/or early childhood strongly predisposes to the onset of asthma. Removal of tonsils and adenoids should be avoided in most cases of asthma, and steroids or ACTH are only indicated in long-

This Review is appearing in three sections, of which this is the second.

continued asthma or status asthmaticus. From Israel, Bergmann[248] states that from a yearly report of a school doctor there were found eighty-one children (1 per cent) with bronchial asthma in a group of 8,024 children. These findings were similar to those of the previous year when, among 4,151 children in Holon, on the seashore, there were thirty-eight with asthma. In Kfar Saba, in the interior, there were fifteen asthmatic children out of 2,687.

Asthma occurs all over the world. From South Africa, for example, Walt[249] studied sixty children over a period of two and one-half years or longer. Besides the routine history, examination and laboratory studies, Walt assessed the personality of the child, his place in the home, and his relationship to his siblings and parents. He advised breathing exercises, advice to the mother on her attitude to the child and to its asthma, and anti-asthma drugs. His results were excellent, especially in those who attended his clinic regularly; psychologic factors were a major cause of asthma in children. [This author did inhalant and food skin tests regularly at first; later he abandoned this technique. Perhaps he stopped skin tests because of poor material. In any case, he abandoned what almost every allergist considers a major method for discovering the cause or causes of asthma and other allergic conditions.]

In 128 asthmatic children in Birmingham, England, Smith[250] reports as follows: roentgenograms rarely revealed any significant hilar congestion or transient shadows. Few of the children in this newly-formed clinic had had any previous therapy despite the fact that more than 50 per cent had had asthma for more than five years. The ratio of boys to girls was about three to one; from five to fourteen about even. There was a positive family allergy history in 70 per cent, and some associated allergic condition in about two-thirds. The income level and family size bore no relation except in cases due to infection, where a much higher proportion (50 per cent) came from poor and overcrowded homes. House dust, cotton flock, horse hair and feathers were responsible in 64 per cent. In 41 per cent other factors were also important, but pollen caused asthma in only 3 per cent; infections in 14 per cent; foods in 5.5 per cent; emotions in only 4 per cent; and unknown etiology in 9.5 per cent. Smith rightly does not believe that emotions or infection alone can cause true bronchial asthma; there must be an allergic sensitivity, obvious or hidden. He stresses the value of skin tests, but interpretation requires experience and clinical corroboration. As regards therapy, 40 per cent required some form of hyposensitization plus careful home inhalant control (a health visitor is attached to the clinic and is employed full time on this work). His results with those who have had sufficient therapy for at least six months: marked improvement occurred in 72 per cent; partial in 19 per cent; no improvement in 9 per cent. [This is a good clinical paper. We especially commend the use of someone to inspect homes.]

Eosinophilia in children has been discussed by Stafford.[251] In 674 nonallergic children, the average eosinophil percentage was 3.2, but in 145 of these (17 per cent), a percentage of 6 or more was observed. This eosinophilia was unexplainable, but perhaps related to some future allergy. In a group of 187 allergic children, representing 21.7 per cent of all the children, the average percentage observed was 6.9 (in fifty cases of asthma, 9 per cent; in sixty-two with hay rever, 6.1 per cent; in twenty-five with perennial allergic rhinitis, 4.7 per cent; in thirteen with atopic dermatitis, 5.7 per cent; in nine with urticara, 6.1 per cent;

in eight with gastrointestinal allergy, 6.8 per cent; in three with Loeffler's syndrome, 12 per cent; and in three with migraine, 4.5 per cent. [Our own average of eosinophilia in 459 cases of asthma of all ages was 5.9 per cent.]

Flensborg,[252] from the municipal Out-Patient Clinic for Allergic Diseases in Children, Copenhagen, reports on 853 children with bronchial asthma or asthmatic bronchitis; 573 boys (67 per cent); 280 girls (33 per cent). Scratch tests were more frequently positive as age increased. House dust, for example, was only positive in 1 to 2 per cent in the first two years of life, but positive reactions increased to 64 per cent between twelve and fifteen. Next to house dust came feathers, cow hair, cat hair, horse dander, composite pollens, trees and molds. Reactions to foods decreased and increased with advancing age: 7 per cent in the first two years; 4 per cent at ages three to five; 1 per cent ages six to eight; then 3 per cent, ages nine to fifteen. He rightly urges that asthmatic children should be re-tested annually, especially if therapy has been unsatisfactory.

The diagnosis of asthma, says Buffum,[253] can be made when a child wheezes and is allergic and other causes of wheezing are excluded. A chest roentgenogram should be made to rule out pneumonitis, tuberculosis, foreign bodies, and heart disease. If the baby wheezes continuously and treatment is ineffective, one must search for a congenital defect of the blood vessels or trachea and for a foreign body. In some cases definite diagnosis cannot be made for weeks or months.

Rapaport et al[254] tested 100 allergic children, aged four to fourteen, with an electrical pneumotachograph, a device for recording the instantaneous linear time rate of change in ventilation of the lungs. It consists essentially of a prime mover and a recorder. The tests were made chiefly on asthmatic children before and after epinephrine, also on controls. The tests were easy for the children because there is no mechanical interference with breathing. The authors believe this machine is valuable in the differential diagnosis of asthma in children who have repeated pulmonary infections with wheezing; it is also good as regards the prognosis of asthma.

Damgaard[255] did provocative experiments on 512 children with bronchial asthma or asthmatic bronchitis, with positive skin tests to one or more allergens. Only children under three were tested, and on these he did 1933 experiments (1,163 by inhalation, 770 by sniffing). Of the 512 children, 62 per cent gave positive reactions to one or more allergens. Of the 1933 experiments, results were positive in 43 per cent. The highest percentage of reactions was to horse dander, 73 per cent; grass, 54 per cent; dust, 52 per cent; molds, 52 per cent. He advises both the sniff and inhalation tests, and found good agreement between these tests and the history, as well as with skin tests. For example, the provocative tests were positive in 24 per cent of children who gave a doubtful skin test; in 38 per cent with one-plus; in 53 per cent with two-plus and in 60 per cent in those with 3-plus reactions. When powerful reactions are anticipated, Damgaard prefers the inhalation method, rather than the sniff, but adrenalin must be available.

Asthmatic bronchitis in children is always a problem, especially as regards the etiology (infectious or allergic). Watson,[256] in a survey of 1500 consecutive cases in a pediatric practice made the diagnosis of asthmatic bronchitis in twenty-three. All of these had negative family allergy histories, and most had fever, cough, wheezing and other rales. These children were followed for five to seven years; eight developed asthma

(40 per cent); an additional 25 per cent developed other allergic disorders; the other 35 per cent so far had no allergic stigmata. Möller[257] followed 219 infants who were admitted to the Children's Hospital of Gothenberg, Sweden, between 1934 and 1946, and were re-studied in 1954. All had been admitted with so-called "asthmatoid bronchitis" in their first year of life. The observation period for 50 per cent of these children was twelve years or more. Results: 5½ per cent had asthma by 1954; 15.5 per cent bronchitis; 79 per cent were asymptomatic, and in all of this group the "asthmatoid bronchitis" in the first year of life was usually the only episode. In such cases, therefore, the prognosis with respect to asthma is good. In commenting on this article, Glaser agrees, but in his experience recurrent attacks of "asthmatic bronchitis," if attacks persist, are practically always followed by bronchial asthma.

In another group of 166 Swedish children, Herlitz[258] states that "recurrent catarrh of the upper respiratory tract" occurs chiefly in early childhood, but usually after the age of six months. The onset generally follows infections from the environment; the disease is apt to be protracted, with frequent exacerbations. The mucosa is swollen, either red or pale, and the pharynx looks granular. Eosinophilia is rare in the blood or nasal secretion, and there is no special relation to foods or inhalants. Low fever is often present, and the stubborn cough of pharyngeal type is very distressing. Over a period of four years this group was compared with a control series, similar but without this "catarrh." The incidence of presumptive allergic affections in parents and siblings in the first group was 23.2 per cent, as compared to only 6.1 per cent in the control group. Bañeres Vall,[259] from Barcelona, also notes that asthmatic bronchitis is frequent in childhood and records the importance of allergy as a cause. Despite the fact that potassium values are frequently increased, paradoxically good results are obtained by giving potassium salts.

Other papers dealing with asthma in children are more general. Clein[260] emphasizes that allergic cripples usually result from neglected allergic problems. Allergic diseases affect about one-third of pediatric patients. Skin testing is an important procedure and is necessary in about 50 per cent of allergic children. Elimination, avoidance, and desensitization are the most effective and permanent parts of the long-range treatment. Clein also discusses early recognition, the mechanism, symptoms, the "allergic cold," the "allergic cough," prophylactic infant feeding, environmental control, and specific and symptomatic therapy.

Acute asthma in children can be cared for at home, says Levin,[261] provided the home is dust-free. He outlines medication, including ACTH and steroids, where necessary. Children with status asthmaticus, however, should be hospitalized. Ratner et al[262] emphasize that infants with allergy should be skin-tested and studied comprehensively so that normal physiology may be restored and allergic reactions in later years prevented or shortened.

Wright[263] notes that the prognosis for asthma in children is generally good. For many children it is a temporary or infrequent disturbance that need not interfere with a normal life. Care should be taken that therapy does not rob the asthmatic child of this opportunity; a psychiatrist may be necessary for the few whose asthma becomes chronic and who have an emotional component.

Joos and Ellis[264] followed 100 children whose asthma began at an average age of 4.4 years. Bacterial sensitivity was the chief cause in eighty-three cases, with positive skin tests for bacteria; in this group,

forty-four had attacks which were provoked by upper respiratory, tonsil or sinus infections. In many cases the attacks ended when the infection was controlled. Tyral® (200 mg tyrosine, 2.5 mg pyrodoxine hydrochloride, 10 mg niacinamide) gave excellent results; the authors believed this mixture aided synthesis of adrenalin in the body. On a long-term basis they obtained 61 per cent good results in the whole group. [This is considerably less than results obtained by other workers, including ourselves. We believe that overemphasis on bacterial sensitivity lessens the percentage of success. The best results are undoubtedly obtained by careful elimination, with or without hyposensitization, as necessary. Vaccines at times are useful.]

Fontana[265] points out that the belief "children will outgrow their asthma" is still unfortunately prevalent and is responsible for serious complications which may result in irreversible changes. Prevention is of utmost importance. Both parents and physicians must have a working knowledge and awareness of allergic problems in childhood. Tonsils and adenoids should not be indiscriminately removed.

Kaufman,[266] in discussing allergy in infancy and childhood, gives a long list of symptoms and diseases which he considers suggestive of allergy. His list is chronologic, beginning with hiccough *in utero* and hyperactive fetal movement, and followed by a large number of conditions, e.g., scleroderma, geographic tongue, anorexia, convulsions, and others. [In this list are many symptoms or diseases in which allergy has *not* been proved; over-enthusiasm regarding allergy may not be beneficial; yet we admit that we must look to allergy in some ill-defined conditions.]

Glaser[267] discusses prophylaxis of allergic diseases in the newborn. Pregnant women should avoid large amounts of egg and cheese. He urges breast feeding, as breast-fed babies have only one-seventh as much chance of developing eczema as do those bottle fed. If breast feeding is not possible, the baby should be started on soybean or meat-base milk substitute.

Dees,[268] in discussing management of asthma in children, notes that treatment with antibiotic drugs is frequently inadequate, as when only one injection is given and explanations to parents are often vague. The diagnosis is not always easy, as one must rule out such conditions as foreign bodies, cystic fibrosis and tuberculosis. Parents often do not recognize that frequent colds in their children are usually due to allergy; nasal-smear-eosinophilia in such cases is diagnostic. Walker[269] has a good general paper on the allergic child.

ASTHMA IN THE OLDER AGE GROUP

Rose, Shires and Alyea[270] point out that elderly individuals frequently complain of fatigue and lack of endurance. Those with ailments which require physical rehabilitation exhibit reduction in efficiency of pulmonary function so frequently as to warrant the presence of hypoxia. Specific retraining efforts for proper breathing coupled with mechanical efforts to increase pulmonary air flow improve the efficiency of external respiration. Improvement is both physical and psychic.

Slepian and Reicher[271] note that in elderly persons who are allergic since childhood, symptoms tend to diminish with increasing age, and at times may disappear, regardless of specific treatment or general allergic management. They theorize: (a) Specific sensitivities may have limited durations and therefore wear out after years. (b) Sensitivity may develop to new substances and therefore causes a different type of allergy.

(c) The allergic response is usually characterized by explosive or vigorous action; in most older persons cells may no longer support such a vigorous immunochemical reaction.

Stuppy[272] has a fine paper on what he calls "Nonallergic Bronchial Asthma," a title he borrowed from Alexander.[273] The latter noted that many patients with asthma failed to obtain relief under rigorous environmental and dietary control of allergenic substances known to cause allergic asthma. These patients also failed to show evidence of allergic hypersensitivity by the usual methods of cutaneous testing and passive transfer. Stuppy states that "onset of asthma after age forty is most likely nonallergic when no specific allergens can be demonstrated," but he adds that exceptions occur so that differentiation on the basis of age alone is not reliable. "In the nonallergic asthmatic patient who is older, the attacks are more severe and prolonged, frequently leading to the development of complications, including chronic emphysema and cor pulmonale. Most of the patients with intractable asthma or status asthmaticus are included in this group, which comprises the majority requiring hospitalization for treatment. Prognosis in the allergic patient is more favorable under proper management, in that identification and elimination of offending allergens and use of hyposensitization procedures may effectively control the asthma before serious complications develop."

Eosinophilia is present in many cases in the blood, sputum and nasal secretion, though less in this "nonallergic" type of asthma. "Treatment for the attack is symptomatic and consists of measures for relief from the bronchial obstruction. Effective preventive treatment of associated bronchopulmonary infection through long-term use of antibiotics materially reduces the severity and frequency of asthmatic attacks, thereby preventing or arresting the development of pulmonary complications." [We object to the title "nonallergic bronchial asthma." The title "asthma" has been used to include any condition in which wheezing occurs, even from a foreign body. The title "bronchial asthma," however, should be used only for the allergic type of asthma even though in some cases the allergic factor cannot be demonstrated. The danger in the title "nonallergic" lies in the implication that one should forget all about allergy and should just treat the patient's symptoms.] Rowe,[274] Tuft[275] and others have insisted that many in this older group are really allergic even when skin tests are negative. [We have frequently found positive tests in older patients because we carry out a large number, both by the scratch and intradermal methods. A small reaction in an older person may be equivalent to a four-plus reaction in a youngster.]

Unger[276] also discusses chronic bronchial asthma in the older age group. Actually, this condition is not very different from that in younger patients. As one grows older, the complications become more frequent and complete clinical relief less likely. The recent introduction of steroids, however, has reduced mortality to almost nil.

Unger states that "bronchial asthma is an allergic condition characterized by wheezing, dyspnea, orthopnea and cough. It may be paroxysmal or chronic, and it is usually associated with a seasonal or nonseasonal allergic type of rhinitis, and with a partial obstruction of the lower air passages. He objects to Rackemann's[277] "intrinsic asthma" because, as stated above, acceptance of this title inclines one to give up further search for an allergic cause. "A recent case in an older man is interesting," says Unger, "because by allergic tests we found the cause, and by avoidance brought prompt and prolonged relief. Mr. F. H., aged fifty-six,

a retired boilermaker, reported September 22, 1947, because of severe asthma for ten years. He suspected milk, tomatoes and exertion as the cause. Examination revealed marked wheezing all over both lungs and fluoroscopy revealed some lessening of diaphragmatic excursion. There were 12 per cent eosinophils in the blood. The rest of the laboratory findings were normal. Skin tests had to be done by passive transfer because he had marked von Recklinghausen's disease. Sixty-four tests were done and only one gave a marked positive reaction. An extract of karaya gum was repeatedly strongly positive, with negative control tests. The patient was using a dental adhesive containing karaya gum because he had an upper denture. This gummy powder was removed and the asthma promptly disappeared and has not returned. This case illustrates allergy to a rather weak allergen which is widely used but is not apt to be considered. Had we not done skin tests we would probably have missed the correct cause."

In this article is a list of allergens which relate to occupational asthma and rhinitis, also a discussion of contributory factors, e.g. psychogenic and infectious. Also discussed are the pathology, pathogenesis, autopsy findings, symptomatology, complications, associated conditions, diagnosis, differential diagnosis, and preventive, specific and symptomatic therapy. It is especially important in older asthmatics to avoid the use of morphine, Demerol®, and hypnotics. Alcohol and aspirin (except in aspirin-sensitive patients) can be used in this age group. The prognosis in older asthmatics is much better in those who have an associated nasal allergy, as distinguished from those who slowly develop nonallergic emphysema, with or without wheezing.

Hurwitz[277A] has a good differentiation between what he calls "allergic" and "nonallergic asthma." His table follows:

DIFFERENTIAL DIAGNOSIS OF ALLERGIC AND NONALLERGIC ASTHMA

Allergic	Nonallergic
History	
Familial tendency to allergy	No familial tendency to allergy
Other allergic manifestations common	Other allergic manifestations unusual
Appearance before middle life	Occurrence more common after middle life
Attacks sudden, unprecipitated	Attacks usually initiated by cold or bronchitis at a time of year when bronchial infections are common
Attacks usually recurrent	Single attacks common
Persistence of slight symptoms between attacks	No residual symptoms after attack
Inhaled substances or foods frequently causative	No relation to inhaled substances or foods
Itching of conjunctival, nasal, and pharyngeal membranes	No itching of mucous membranes
Constitutional reactions	Status asthmaticus
Examination	
Visible mucous membranes pale, glistening, edematous	Visible mucous membranes hyperemic, red
Thin, watery mucoid nasal discharge, mucoid sputum	Mucopurulent nasal discharge and sputum
Predominance of eosinophils in smears of nasal or bronchial secretions	Predominance of polymorphonuclear leukocytes in smears of nasal or bronchial secretions
Sinus involvement of hyperplastic type (nasal polyps)	Sinus involvement of purulent type
Slight or no bronchial markings on lung roentgenograms	Peribronchial thickening and, with chronic disease, emphysema on lung roentgenograms
Skin tests positive	Skin tests negative
Urticaria, eczema, or other allergic manifestations	No urticaria, eczema, or other allergic manifestations

DIAGNOSIS

Several papers discuss the direct diagnosis of allergic diseases, including bronchial asthma. Sherman[278] has a long article on "Diagnostic Methods For Allergic Diseases"; readers should study this article in its entirety. "The many different methods utilized in the specific diagnosis of allergic sensitizations reflect the fact that no one approach may be relied upon to furnish satisfactory results in all cases. While skin tests of various types play an important part in such diagnosis, it is important to realize that they are only one aspect of the study, to be evaluated in conjunction with the history and careful examination of the patient for evidence of infective factors. The conclusions reached must furnish a reasonable explanation of the time and circumstances of symptoms, and reflect sound judgment as well as technical skill."

Sherman discusses the various methods of skin tests; he prefers the intracutaneous technique as being more accurate than either the scratch or prick methods. He admits the dangers of his method but claims that experience lessens any real danger almost to the vanishing point. He further says that "because of differences in safety and accuracy some workers in the field prefer the intracutaneous test and others the scratch test, while a few employ both methods, doing scratch tests first and intracutaneous tests later. It is the opinion of the author that the physician relatively inexperienced in the field may well employ the safer scratch method but that well-trained workers will gain more satisfactory information from the more accurate intracutaneous method, using the scratch tests as a preliminary only in patients believed to be unusually sensitive to a particular antigen, or when using a new antigen with which they are not thoroughly familiar." [This statement, of course, is entirely unacceptable to many of us who have watched the study of allergy grow, and who have seen and read about fatalities and near fatalities from the exclusive or almost exclusive use of the intracutaneous technique. We contend that no one, not even the most expert, can always determine the degree of sensitivity of his patient. Cottonseed-protein-sensitive patients, for example, rarely know of this sensitivity unless told about it by an allergist. Intradermal testing with this potent extract can be very dangerous. Sherman is also in error when he states that "a few employ both methods." Actually, more and more allergists, including ourselves, make scratch tests first; if we need more information, we follow with intradermals, and when scratch tests are negative we do not fear to do intradermal tests with the same proteins. Swineford[279] had two unfortunate systemic reactions from intradermal injections of mustard extract. He preceded his intradermal testing with a large series of scratch tests, but in these two patients mustard extract was not one of those previously tested by the scratch technique. Swineford urged scratch tests first, then intradermals, if necessary.]

Peshkin[280] also discusses skin tests and emphasizes the various pitfalls. In the same issue an editorial[281] agrees with Peshkin's statement that injudicious use of skin tests is harmful. Skin tests with food allergens are, on the whole, of less value than with inhalants. False positive or false negative tests can occur. Hughes[282] points out that a positive skin test may be inaccurate because of avoidable or unavoidable errors in technique. Avoidable errors may follow contamination of test solutions and needles used with other extracts; unavoidable error may occur from contamination of raw materials from which the extract is made, e.g. there may be as much as 5 per cent contamination in pollens gathered for extracts.

Positive skin tests may denote past, present or future allergy. In some youngsters positive skin tests may occur but seem to disappear spontaneously. In individuals with positive skin tests which do not relate to exposure hyposensitization is not necessary.

Ogilvie[283] adds that skin tests are merely diagnostic aids. Extracts are not too well standardized, he notes, but he agrees that when used with discrimination in selected cases and with recognition of its admittedly serious limitations skin testing can be useful in diagnosis. Used routinely without selection it is quite likely to mislead and most unlikely to be helpful, however much it may impress the patient or the parent. [We agree with his thought that skin testing must be carefully done by someone with experience who can correlate these tests with clinical facts. This author, however, seems to have only a lukewarm interest in skin testing.]

Tuft et al[284] note diminishing response to skin tests with advancing age, especially after ages fifty to sixty. Reactions to food allergens were employed on individuals known to be sensitive to those foods. Skin reactions to histamine did not decrease greatly until after the age of sixty. [We agree with these observations. These are important both in direct testing and in passive transfer work. Recently we did passive transfer of serum from a patient who almost died after ingestion of candy containing Pignola nuts. Direct scratch tests with an extract of these nuts were strongly positive. Passive transfer tests on one recipient aged thirty-two were also strongly positive. A few days later when this recipient ate some of these nuts the sensitized sites all itched and became markedly inflamed. The second recipient was sixty-five years old; his reactions by both methods were about 50 per cent of those of the younger man. Hence, it seems wise to choose young nonallergic adults for passive transfer tests.]

Walzer[285] emphasizes diagnostic procedures, including the need for a careful, detailed history and examination, skin tests, ophthalmic and nasal tests, and environmental and dietary trials. Steele[286] has a point-scoring system for diagnosis of the allergic state. He gives from one to three points for findings which are suggestive of allergy, e.g. nasal polyposis, wheezing, family allergy history, eosinophilia and positive skin tests. A score of fifteen points is practically unobtainable, but arbitrarily, at least four points are considered essential for a definitive diagnosis of the allergic state.

Herxheimer[287] advocates wider use of experimental methods for exploring etiology and trying out therapy. (The skin tests should not be the only objective evidence in support of the history). He uses a closed circuit method of testing by inhalation, in which a recording spirometer circuit contains a side circuit from which aerosols of histamine, antigens or antispasmodic agents can be added to the inhaled air. Inhalation of 3 per cent histamine quickly produces attacks of asthma in asthmatic patients; no attacks occur in nonasthmatics unless inhalation is prolonged. His patients inhale allergens and he also attempts to hyposensitize some by repeated inhalations of these allergens. If the patient develops asthma from overdose of allergenic extracts, he aborts the attacks by isoprenaline aerosol.

Latent tendencies to asthma can be detected by pneumatometric studies, says Fuchs.[288] The pneumatometer reveals extremely fine variations in bronchial resistance of a patient after inhalation of only minute quantities of offending antigens, and these variations can be observed at a

stage when clinical symptoms are absent. He believes that his method is far superior to those based on skin tests. The machine has been accurate in 66 per cent of his cases. Von R. Hoigne et al[289] found that if the serum of an allergic patient is mixed with the allergen there occurs a minimal turbidity within a definite dilution range. This reaction can be measured by means of a sensitive nephelometer, and is due to the interaction of a specific dialysable factor obtained from sensitized serum (Factor 1), a nonspecific nondialysable portion (Factor 2), and the allergen.

DIFFERENTIAL DIAGNOSIS

An excellent outline of differential diagnosis was given students by Koelsche;[290] it is given in full.

De Gara[291] also discusses differential diagnosis, with special reference to (a) mechanical conditions, e.g. foreign bodies, thymus, substernal goiter, neoplasms, aneurysm, and thoracic deformities; (b) infections or inflammatory diseases, e.g. tuberculosis and pneumoconiosis; (c) cardiac and circulatory conditions, e.g. cardiac dyspnea, cardiac asthma and periarteritis nodosa; and (d) miscellaneous conditions, e.g. psychosomatic and toxemic. Ellis[292] differentiates between cardiac and pulmonary dyspnea. Banyai[293] also writes about the differential diagnosis of chest diseases, and he does this nicely by discussing pulmonary hemorrhage, cough, chest pain and dyspnea. "Accurate diagnosis is the key to successful treatment of chest diseases. Thus, it is mandatory that the physician approach this problem with a wide orientation in medicine, an inquisitive mind, and sound logic. The welfare of the patient demands that the physician take full advantage of diagnostic aids derived from x-ray and laboratory studies. One should also avail himself of other diagnostic methods, such as skin testing, biopsy, bronchoscopy, and cardiorespiratory function tests as circumstances may require. It is inexcusable to omit a thorough physical examination." In another article Banyai[294] has three excellent tables on differentiation between cases in which hemorrhage, wheezing and chest pain are prominent.

Emphysema has already been discussed. In addition, Farber, Wilson and Smith[295] outline therapy for the emphysema which occurs in chronic bronchitis and asthma. Seven headings are mentioned: (a) liquefaction of sputum with iodides and humidifiers; (b) bronchodilators; (c) intermittent positive pressure breathing valves; (d) antibiotics to control infection; (e) breathing exercises; (f) various other specialized techniques; and (g) techniques for preventing respiratory acidosis during acute phases.

PNEUMOCONIOSES

The various types of pneumoconioses continue to intrigue us, both from the point of view of complications of bronchial asthma and from that of differentiation. We have selected only a few of the hundreds of articles on this subject; our apologies go to those whose papers have been omitted because of lack of space.

Sander[296] has done a great deal in this field. In an illustrated article he discusses the benign pneumoconioses, e.g. siderosis (iron dust), anthracosis (carbon particles), barium and tin. He points out their differentiation from such serious lung infiltrations as occur in silicosis and beryllosis. The benign particles may cause fine stippling on chest x-ray films. "The evidence is sufficiently clear to make it advisable to consider the possibility of benign pneumoconiosis in the differential

DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA

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I. Respiratory System

A. Larynx
1. Inflammatory lesions
2. Spasm caused by:
   (a) Rickets
   (b) Tabes
3. Angioneurotic edema
4. Neoplasms
5. Foreign bodies
6. Paralysis of vocal cords
   (a) Postoperative thyroidectomy
   (b) Carcinoma of thyroid

B. Trachea and bronchi
1. Intrinsic lesions
   (a) Bronchitis, acute or chronic (tobacco effect)
   (b) Bronchostenosis
   (c) Neoplasms
   (d) Foreign bodies
2. Extrinsic lesions, that is mediastinal tumors; symptoms caused by pressure
   (a) Substernal goiter
   (b) Aneurysm of thoracic aorta
   (c) Thymoma
   (d) Enlarged tracheobronchial nodes

C. Lungs
1. Pulmonary eosinophilia with:
   (a) Changing pulmonary shadows
   (b) Asthmatic wheezing
   (c) Leukocytosis and blood eosinophilia
2. Emphysema
3. Neoplasms
4. External pressure caused by:
   (a) Pneumothorax
   (b) Hydrothorax
5. Silicosis, history and roentgenographic differentiation

II. Cardiovascular System

A. Cardiac decompensation
1. Story of heart disease
2. Presence of edema
3. Asthmatic treatment ineffective
4. Morphine and digitalis effective
5. Circulation time and venous pressure increased

B. Coronary sclerosis with paroxysmal nocturnal dyspnea
1. Story of angina
2. Attacks of different type, shorter

C. Periarteritis nodosa
1. Increased sedimentation rate
2. Eosinophilia
3. Arteritis
4. Asthma associated

D. Anomalies of great vessels

III. Nervous System

A. Functional or sighing dyspnea

B. Hyperventilation syndrome
1. Often conditioned by bloating, aerophagia, or fear of heart disease
2. May lead to tetany or fainting

diagnosis whenever a fine nodular x-ray pattern with normal hilum shadows is encountered. If this is done with all such cases, the too frequent and always unfortunate misdiagnosis of silicosis may be avoided in at least some cases. It is well always to bear in mind that all that is nodular by x-ray is by no means due to silicotic nodules." Sander believes iron welders rarely develop serious trouble unless they are also exposed to silica, but Charr[297] reported three cases in which prolonged exposure to welding fumes, which contain iron oxide, led to dyspnea and cough. In none of these patients was there any appreciable exposure to silica. In two of these cases biopsies revealed pulmonary fibrosis. Charr states that pulmonary infiltrations can occur in welders, but symptoms are rare.

In a long letter[298] Gough and Heppleston, from the Welsh National School of Medicine, discuss focal emphysema as "a group of dilated respiratory bronchioles occurring in and around a focus of dust such as coal." They agree with Sander and others that "the degree of clinical and physiological disability in simple pneumoconiosis does not correlate with the radiological appearances." They believe that "focal emphysema is due to mechanical overloading of the lung with relatively inert dust."

Schepers[299] says, "Anoxia is the principal factor in the etiology of cor pulmonale which can follow inhalation of various occupational dusts. Among workers in asbestos, quartz, cristabolite, and talc industries, collagen is deposited within the capillary walls. Quartz, coal and graphite cause an accumulation of carbon-laden coniophore cells within the alveolar membrane. Multiple layers of capillaries and collagen are noted in iron miners, asbestos and foundry workers. and welders. The most important vascular changes occur in the small blood vessels."

Eight cases of talc pneumoconiosis occurred in workers who were pulverizing pieces of soapstone in electric mills, according to Alivisatos et al.[300] The disease occurred in six after exposure of sixteen to twenty-four months; in the other two after forty to sixty months. The air was grossly polluted with small talc particles, which were chiefly five microns or less in diameter. X-rays were similar to those found in silicosis, and moderate to severe impairment of pulmonary function occurred in all, with death in one man who had been exposed for six years.

Early bagassosis has been mentioned by Ganguly and Pal;[301] this is an industrial disease caused by the inhalation of bagasse dust, a waste product of sugar cane after the sugar has been extracted. It is used extensively as a raw material for making paper, and three cases are reported for the first time in India. The authors believe the disease is an acute allergic response to the dust which probably contains a protein mixture that acts as an antigen. A bacterial infection is usually superimposed, causing acute bronchiolitis, and patients have fever, cough with tenacious sputum, dyspnea and hemoptysis. The three patients were separated from the factory and they all recovered within three months.

Vanadium is found in all fuel oil, particularly in the residual heavy oil, according to Gordon Thomas and Stiebris, from Australia.[302] Poisoning can occur, as in one of the patients who had been cleaning an oil-burning boiler. During the five-hour task headache, cough and colicky abdominal pains occurred, and hours later itching all over the body, swelling of the lips and smarting of the eyes. Examination at this time revealed bronchovesicular breath sounds with an expiratory wheeze and numerous sibilant rhonchi. Precautions against vanadium poisoning are

outlined. Reed[303] reports that even prolonged exposure to zirconium dust does not seem to affect the lungs.

Wright[304] differentiates silicosis and asbestosis. In the end stages the clinical impairment may be quite similar, but in the earler phases the victim of asbestosis is apt to have an impaired ability to transfer oxygen to the blood rather than impaired breathing ability and ventilation. Small areas of emphysema occur in the tissues of the lung of the typical patient with asbestosis, but the massive emphysema so commonly observed in conglomerate silicosis does not appear to be present in even the severe cases of asbestosis.

A query regarding the management of a case of bilateral pulmonary fibrosis with emphysema, cause undetermined, in a forty-nine-year-old physician, led to these suggestions: antibiotics, as necessary, physical exercise up to the point of tolerance, special breathing exercises and bronchodilators.[305]

Frost and Georg,[306] from Copenhagen, discuss eight cases of "thresher's lung." These occurred in the threshing season, during the first five months of 1955. The grain was mostly barley and was harvested in the wet summer of 1954; the grain was moldy and dusty. In the milder cases dyspnea, cough and fever occurred but soon disappeared. In the severe cases the course was protracted, with persisting dyspnea and extensive roentgenologic changes that led to confusion with miliary tuberculosis and sarcoidosis.

Silo-filler's disease is described by Delaney, Schmidt and Stroebel[307] and by Lowry and Schuman.[308] The first group report two cases of a syndrome manifesting itself as a serious pulmonary disease among certain farmers engaged in ensiling. Those who work in silos may be exposed to inhalation of nitrogen dioxide gas. The fumes which accumulate in corn-filled silos under certain conditions are quite toxic, and can cause coughing, with expectoration of brown or bloody sputum, dyspnea, and chest constriction, along with fever, tachycardia and weakness. Harsh rhonchi or moist rales may be heard, and x-rays may reveal a diffuse mottling. Lowry and Schuman also reported four patients, of whom two died on the twenty-seventh and thirtieth days; the other two also had severe respiratory symptoms, but the disease was halted by intramuscular injections of 10 mg prednisone, three times daily. Both papers stress preventive therapy.

LOEFFLER'S SYNDROME

According to Loeffler[309] this syndrome, characterized by rapidly developing and rapidly disappearing x-ray shadows in the lungs and transient blood eosinophilia, can be reproduced in guinea pigs by ingestion of embryonized eggs of ascarides. The migration of the larvae can be followed from its start in the mucosa of the colon through the liver into the lungs and bronchi. But "it is evident that the ascaris is not the only but probably the most common and most frequent cause of the transient pulmonary infiltrations."

Epstein and Kligman[310] report that of 1,000 patients who received hyposensitization injections of 3-penta-decylcatechol, one of the allergens in poison ivy, seven developed eosinophilic pneumonitis (Loeffler's syndrome). Pulmonary symptoms began eight to forty-eight hours after the last injections, with patchy pneumonitis, leukocytosis and eosinophilia. The authors believe that the pulmonary infiltrates are due to trapping of

eosinophils in the lung and not, as commonly believed, by an allergic pulmonary reaction.

Livingston[311] discusses three cases of pulmonary eosinophilia which occurred in "asthmatic" patients. After nine years of these episodes one died of cardiac failure, and autopsy revealed the gross lesions of periarteritis nodosa (polyarteritis) in almost every tissue. In the second case, thoracotomy was performed seven months after the onset; the lung was studded with nodules; biopsy revealed granuloma with eosinophilic cells. ACTH reduced the fever, and the pulmonary opacities cleared within ten to fourteen days. Mild asthma continued. In the third patient, a boy of thirteen with asthma since infancy, the blood eosinophilia was up to 8,840 per mm and the transient opacities were present.

Diaz-Rivera et al[312] studied thirty-three cases of infiltrative eosinophilia. The disease is not exclusively tropical; it predominates in the white race. It may occur at any age, and onset may be insidious or acute, but, once established, the disease almost always becomes chronic. "Lassitude, weakness, general malaise, weight loss, paroxysmal cough with scanty sputum, slight dyspnea, wheezing respiration and low grade fever" are symptoms of the insidious onset. Acute cases are usually characterized by a violent attack of asthma with fever. "The condition is in many respects indistinguishable from polyarteritis nodosa with diffuse pulmonary eosinophilic infiltrations."

Leckert's[313] patient, a soldier, developed some cardiac symptoms and signs along with his Loeffler's syndrome. He recovered after five months; he was not given ACTH nor steroids. His blood eosinophilia was high, up to 52 per cent.

TROPICAL EOSINOPHILIA

A number of papers have appeared on this interesting condition which we in this country rarely see, but which is frequent in warm parts of India as well as in other tropical and semi-tropical regions. The eosinophilia may be confused with asthma, but one must remember that patients with true allergic asthma average about 5 to 6 per cent eosinophilia, rarely over 20 per cent. Anything higher should cause the clinician to suspect parasites, tropical eosinophilia, periarteritis nodosa, Loeffler's syndrome, or some form of malignancy.

From India come several papers. Sanjvi et al[314] consider tropical eosinophilia to be a form of bronchial asthma, intermittent between the ordinary form of asthma in which there is no mottling on the roentgenogram and less than 30 per cent eosinophils, and the form associated with periarteritis nodosa. Between tropical eosinophilia and periarteritis there is a severe form of tropical eosinophilia associated with pleural and/or joint effusions. Because of the assumed allergic etiology, twenty-five patients were given intravenous ACTH, daily for ten days in doses ranging from 5 to 20 units. The average patient was free from symptoms by the third day of therapy. Good results were obtained in twenty-two cases, but three patients had relapses, and in two therapy was stopped because of albuminuria. Ascariasis was present in three patients. As a follow-up, twenty-one patients were given cortisone for ten days, with doses ranging from 50 to 100 mg daily. In nineteen cases, remission was satisfactory, but, as with ACTH, the duration of remissions was short. Fleeting chest pains occurred in seven cases. The authors believe that neither ACTH nor cortisone can be considered a cure for tropical eosinophilia, although both produce rapid beneficial effects. They suggest that

ACTH initially, followed by cortisone, may offer better long-term results.

Banerji[315] treated ten patients who had the usual cough and wheezing, with or without fever, rhonchi, leukocytosis and high eosinophilia. Instead of giving the usual six to eight intramuscular injections of an arsenical compound, he tried diethylamine acetarsol in an aerosol for eight to ten days. Nine patients showed complete remission of symptoms, but the eosinophilia was only satisfactorily reduced in four. The aerosol did not seem to have any great advantage over parenteral therapy. Ganatra and Lewis[316] state that, although arsenicals have proved effective in tropical eosinophilia, the mode of action of the arsenic is little understood. Preparations for oral use seem less effective than those injected. The clinical and radiologic improvement usually precedes return of the blood count to normal. In their study, thirteen consecutive ambulatory patients were given diethyl-carbamazine and the results compared favorably with those obtained by Carbasone.

Dalrymple[317] reports two cases which occurred more than a year after departure from India. The illness came on thirty-four and fourteen months, respectively, after departure from the tropics; symptoms were mild; x-ray pictures were negative; the course was chronic with vague symptoms, including mild abdominal pains. The most important aspect was the rapid response of the eosinophilia and symptoms to injections of oxophenarsine hydrochloride.

In Levin's case,[318] a thirty-two-year-old veteran was admitted to a Veterans Administration Hospital in 1947. He gave a history of presumable filariasis while in Samoa in 1943. In August, 1945, while aboard ship, he developed nocturnal dyspnea and wheezing "asthmatic attacks," relieved by epinephrine. These continued until October, 1945, when he was hospitalized with a pneumonic process; at this time a 43 per cent blood eosinophilia was reported. Symptoms continued intermittently until early 1947; symptoms were chiefly "asthmatic" but skin tests proved negative. The white counts ranged from 13,500 to 24,000, with 20 to 68 per cent eosinophils. Skin tests and complement fixation tests for filiriasis were strongly positive. He was given four injections of Mapharsen with prompt relief of all signs, symptoms and laboratory abnormalities, and he has remained normal except for a persistent positive skin test for filariasis. The author believes that tropical eosinophilia and filariasis are related, and that arsenic is specific in therapy.

From Recife, Pernambuco, Brazil, comes a good paper by Coutinho.[319] From a study of eighty patients, he describes tropical eosinophilia as a chronic benign process with cyclic nocturnal paroxysms of nonproductive persistent coughing with variable amounts of wheezing and expiratory dyspnea, sometimes preceded or accompanied by loss of weight, fatigue, fever, anorexia, thoracic pains, and upper respiratory symptoms. A diffuse mottling or an accentuation of bronchovascular striations and a hilar enlargement were the usual roentgenographic manifestations. The essential feature was an intense eosinophilic leukocytosis. Other common features were eosinophilic hyperplasia of bone marrow, an increased sedimentation rate, and negative tests for syphilis or any parasitic disease. Twenty of his eighty patients were under twenty years of age.

Coutinho has tried ACTH, cortisone, antibiotics, antiparasitic drugs, antihistamines, and hyposensitization with extracts of dust and mixed molds. Success, however, was much less permanent than can be obtained

in almost all cases by arsenical compounds, e.g. Carbasone. He advises 0.25 gm capsules of Carbasone twice daily for ten days; this schedule is repeated after an interval of ten days. He adds ascorbic acid (250 mg twice daily) to avoid arsenic intolerance or intoxication. If results are not promptly obtained, four to six intravenous injections of oxophenarsine are given weekly. Attempts to transfer tropical eosinophilia to the author and eleven other volunteers failed.

PERIARTERITIS (POLYARTERITIS) NODOSA

This condition is very apt to be confusing both because of its varied etiology and symptoms, and especially because wheezing, dyspnea and eosinophilia are frequently present. Rose[320] recently surveyed 117 proven cases for the British Medical Research Council. The incidence, especially among the elderly, seems to be increasing, and it is apt to occur among patients with rheumatoid arthritis, rheumatic heart disease, and acute or chronic respiratory infections, or as a result of therapy for these. The evidence against drugs is not conclusive, except for a few cases apparently due to thiouracil. In twenty consecutive proven cases in which the patients did not receive cortisone or corticotropin (over a period of three to eleven years), fourteen have died, three still have the condition actively, and the other three appear to have become symptom-free.

A sixty-six-year-old male patient of Larochelle and Julien,[321] was admitted to the hospital because of extreme weakness, emaciation, anxiety and pains in the extremities; symptoms were present for three weeks and the man also had purpura and chronic asthma. He received great relief from intravenous injections of ACTH, and also from oral hydrocortisone, with reduction in his blood eosinophils from 44 to 7 per cent. Four months later asthma and pain in the feet recurred and another course of ACTH was given; in ten days the eosinophilia dropped from 54 to 13 per cent after the patient had received eight intravenous infusions of 20 mg each.

Talbot[322] has an illuminating article on polyarteritis, a term he prefers to "periarteritis nodosa," and its sister condition "systemic lupus erythematosus." He points out the frequency of asthmatic wheezing, the increase in eosinophils, and the temporary relief from corticotropin. Pathergic granulomatosis is described by Fienberg[323] as an typical periarteritis nodosa or a respiratory-renal type of polyarteritis nodosa. The condition has also been called Wegener's gramulomatosis, but terminology seems to be in a state of confusion. Recently, because of the appearance of these lesions in asthmatics, another title has been suggested, that of "allergic granulomatosis." Four patients with similar symptoms, ending fatally, have been described by Leggat and Walton[324] under the title of "Wegener's granulomatosis." The condition seems most common in the fourth and fifth decades and the first symptoms are usually respiratory.

[Confusion still exists in differentiating tropical eosinophilia, Loeffler's syndrome, and periarteritis nodosa. There are overlapping features and the exact etiologies of these three are still unknown. Eosinophilia seems highest in tropical eosinophilia, less in Loeffler's syndrome and least in polyarteritis, but even this distinction does not always hold true and eosinophilia can be absent in polyarteritis. On the whole, the eosinophilia is usually much higher than in the ordinary case of bronchial asthma with which they may be confused, because of the blood counts and the frequent presence of wheezing and dyspnea.]

MUCOVISCIDOSIS

This condition, formerly known as cystic fibrosis or fibrocystic disease of the pancreas, occurs much too often, and since wheezing and dyspnea usually are present it must be differentiated. Di Sant'agnese[325] points out that it is a generalized hereditary disease of children in which the pancreas, lungs, sweat glands and frequently the liver are affected. A variable degree of bronchial and pulmonary involvement is almost always present and usually dominates the clinical picture and determines the fate of the patient. The basic trouble is mechanical in that failure to remove bronchial mucus causes widespread obstruction and predisposes to secondary infection. The diagnosis is based on: (a) the absence of pancreatic enzymes in the stools, along with large bulky and foul stools; (b) x-ray films which show emphysema with "chronic bronchopneumonia"; (c) abnormal sweat with salt depletion in hot weather, and much increase in the electrolyte content of sweat; and (d) the fact that siblings often have a similar condition. Early diagnosis followed by administration of antibiotics (usual organism is *Staphylococcus aureus hemolyticus),* before permanent bronchial damage occurs, in addition to appropriate dietary measures, offer the best chance for survival. [The prognosis is very serious, but we have one youngster now who has lived about a year since the diagnosis was made and he is symptom free.]

An editorial[326] discusses cystic fibrosis. It is rare in Negroes and never seen in Mongolians, but occurs in about one in 600 live births in the white population. In most but not all infants with this disease, pancreatic deficiency is present from birth, as shown by a marked decrease or absence of amylase, lipase, and protease in the duodenal fluid. The pancreatic ducts and the bronchioles tend to be obstructed. Obstructive emphysema usually occurs with resultant bronchopneumonia, clubbing of the fingers, cyanosis, respiratory acidosis and cor pulmonale. Many of such patients have been misdiagnosed as "intractable asthmatic bronchitis." The condition has also been discussed by Howes,[327] Keats,[328] Moloshok and Moseley,[329] and in another editorial.[330]

MISCELLANEOUS DIAGNOSTIC PROBLEMS

Bronchial asthma may also have to be differentiated from less frequent conditions. Salén[331] says that the "coughing disease," in which no definite findings for the diagnosis of asthma are found, nevertheless is probably on an allergic basis. House dust seemed to be the cause in two of his eleven patients, and eosinophilia can occur. Hearn[332] agrees that the cough of "chronic bronchitis" is closely related to that of asthma and is allergic rather than infective. In about 40 to 50 per cent of his cases contact with feather mattresses was frequent and important. In these cases the onset was insidious, without fever, but with cough, white frothy or thick grey sputum, followed by nocturnal wheezing and increasing dyspnea on exertion. [These two reports are strongly suggestive of what we call "allergic bronchitis," a condition which we believe frequently precedes the onset of bronchial asthma.]

Bronchial adenomas occurred in seven of 100 pulmonary tumors, according to Holle and Schautz.[333] They usually begin in early life, grow slowly, and usually arise in the larger bronchi, and grow in the wall or into the lumen as a pedicle. Cough, asthmatoid attacks with wheezing, increased amounts of sputum, and small hemorrhage can occur. Histologically, these adenomas are of either carcinoid or cylindroma type. The authors urged radical removal, and in their seven cases they per-

formed one pneumonectomy, two bilobectomies, two lobectomies, one segmental resection and one resection of a bronchus. Biocca[334] writes about adenomas at the tracheal bifurcation. Malignancy is present in about two-thirds of the cases, and progressive dyspnea, spasms of cough, and "asthmatic" crises are common.

The so-called "Hamman-Rich" syndrome, which is a diffuse interstitial fibrosis of the lungs, is further described by de Costa and Torres.[335] It is a rare condition, most frequent between forty and fifty, with uncontrollable cough, clubbed fingers and toes, acute dyspnea, and acute cyanosis that do not respond to any treatment. The disease is rapidly fatal. Death is due to cor pulmonale with cardiac decompensation or to intercurrent infection. Another rare condition, pulmonary muscular hyperplasia (muscular cirrhosis of the lungs) is described by Rubinstein et al.[336] The lungs have the hobnail appearance seen in cirrhosis of the liver. The cause is unknown and the disease itself is chronic.

Holman[337] reports two patients with asthmatoid symptoms. One was relieved by removal of a chicken bone after two previous bronchoscopies had failed; the wheezing here was bilateral. The other patient's bilateral rales were overcome when a piece of tin foil was removed from the right main stem bronchus. [Inhalation of foreign bodies is a not infrequent cause of dyspnea and wheezing. One should remember that metallic objects usually cause unilateral wheezing unless the obstruction is high up; but vegetable objects, e.g. peas, peanuts and corn kernels, tend to cause bilateral wheezing which strongly resembles that of bronchial asthma. In this vegetal group, x-ray findings at first are usually negative; bronchoscopy is urgently necessary in all doubtful cases, as the absence of a history of inhalation is of no value in infants and young children.]

Hemming[338] reports severe bronchospasm characteristic of bronchial asthma among a group of ninety-three Indians in Fiji. These were infested with ascaris. Bronchopneumonia also occurred in many, especially in those who were malnourished. One must therefore consider ascariasis in the differential diagnosis of bronchial asthma and bronchopneumonia in areas with such infestation.

Wheezing, decreased breath sounds and dyspnea in an eleven-month-old girl were traced to a bronchogenic cyst by Smid et al.[339] Groves and Effler [340] reviewed twenty-seven patients (twenty-nine to seventy-six) whose broncholithiasis was discovered in the Department of Thoracic Surgery of the Cleveland Clinic Foundation. Bleeding, cough, and bronchial obstruction with fever, wheezing, dyspnea and pain in the chest were the most important symptoms. Another rare pulmonary condition has been entitled "progressive pulmonary dystrophy" or the "vanishing lung" by Heilmeyer and Schmid.[341] Five cases are described in which pulmonary lobes or parts of lobes were found to be completely destroyed. Lipid pneumonia can result from ingestion of large amounts of mineral oil, according to Mason.[342]

Sarcoidosis is discussed by Ray.[343] The diagnosis is based on the clinical picture and the exclusion of tuberculosis, fungus infection and such pneumoconioses as beryllosis. Only cortisone has proved effective, says the author, but the course of sarcoidosis is usually so mild that steroids are to be used only in the more severe cases.

Acute obstructions of the upper respiratory tract are frequently seen in the admitting rooms of general hospitals. McDowell and Maloney[344] point out that the obstruction may be due to infection, neoplasm, mechanical causes, trauma, nerve involvement, et cetera. The characteristic symp-

toms are the indrawing of the supraclavicular spaces, the labored inspiration, stridorous breathing, cyanosis, rapid weak pulse, fatigue, and the anxious faces of such patients. When these signs are present, bronchoscopy should be done at once if the attending physician is skilled in passing the bronchoscope; if not, an immediate tracheotomy must be carried out to save the patient's life. One should err on the side of too early and too many tracheotomies, rather than too late and too few.

Bronchopulmonary symptoms can also occur from toxoplasmosis, say Mercier and Pangalos.[345] Ocular symptoms are frequent. Rios[346] also writes of fungus infections of the bronchi and lungs. The importance of accurate mycological technique is stressed.

Vugrincic[347] believes that "cardiac asthma," denoting paroxysmal attacks of "asthmatic" breathing, is due to insufficiency of the left heart and consecutive pulmonary congestion. Some striking peculiarities in the symptoms remain unexplained, e.g. the occurrence of cardiac asthma only in the recumbent position, its appearance only in incompetence of the left heart caused by failure of the left chamber, and its infrequent occurrence in patients suffering from defects of the mitral valve. The author believes that these peculiarities are best explained by the influence that intra-arterial hydrostatic pressure exerts on the work of the left ventricle. Baronofsky and Cox[348] have a good article on pulmonary edema. Increased filtration pressure in the lung capillaries is the cause, they say.

In a symposium on the "common cold" the viewpoints of the internist, otolaryngologist, allergist and pediatrician are presented.[349] Malcolm Miller gives the allergist's ideas, with special emphasis on the local appearance of the nose and the finding of nasal eosinophilia.

TREATMENT OF BRONCHIAL ASTHMA

The goal in the treatment of bronchial asthma consists of (1) preventing the first attack if possible, and (2) of returning the asthmatic patient to normal (objectively and subjectively), or as close to normal as possible.

The "allergy-minded" doctor is aware of at least four basic evolutionary phases in the treatment: (a) prevention of the development of asthmatic symptoms in the potentially asthmatic individual; (b) avoidance of known allergens; (c) hyposensitization, to increase an individual's tolerance to known and important allergens which cannot be avoided; (d) the use of drugs for symptomatic therapy to control the patient's symptoms either until specific therapy has become effective, or when the individual is overexposed to his known allergens, or when the specific allergens have not been discovered.

Prevention.—Glaser,[17] in his book, recapitulates his approach with his reasons for preventing the development of allergic manifestations in the potentially allergic child. The concept is based on the idea of minimizing the allergic load to the unborn baby by minimizing the mother's exposure to the more strongly sensitizing food allergens. The infants should be given synthetic vitamins, instead of fruit juices, et cetera, and a meat base formula instead of milk. [His basic concepts are logical and his results certainly warrant consideration. The main question, however, is to determine when to apply his routine. Since no one can know which children of allergic parents will become allergic, is it practical indiscriminately to make such families slaves to this preventive routine? Certainly, the home environment should be spic and span from the allergic

viewpoint, e.g. the banning of household pets, feather, cotton and kapok pillows, stuffed toys, and ordinary rug pads and soft furniture stuffed with ordinary materials.]

Elimination.—We found no papers published which concerned themselves purely with avoidance of specific household allergens. There is a need for a study, in which one group of asthmatic patients would be treated only by controlling the home environment, and another group by both household control and hyposensitization. Many of the papers on treatment included general remarks on the preparation of the allergen-free home, but nothing new was introduced. The several papers on air conditioners and air filters were mainly concerned with hay fever pollens.

We should remember that many foods belong to botanical groups, e.g. the legumes, fish, citrus fruits and the gourds. It is frequently advisable to urge patients who are allergic to one member of such a group to avoid not only the particular food, but also all the other members of that group.

As regards inhalants, we stress again the need for strict supervision of the patient's environment to make sure that orders have been carried out. House calls are often necessary to ensure complete obedience to orders. Many families are loath to part with a favorite cat or dog even though this pet has been shown to cause the asthma.

Hyposensitization.—Garnett,[350] on the concept of hyposensitization, states that "every experienced allergist in the room has a different program that works better for him." He recommends that we should hyposensitize people only when they cannot successfully avoid the specific allergens; and we should only attempt hyposensitization to inhalants that cause important symptoms. [We emphatically agree. There is a common misunderstanding about the significance of skin tests especially by patients who believe the role of the allergist is simply to do skin tests and give injections. Each patient is different, and his response to skin tests must be evaluated and correlated with his history and physical examination. This is especially so when the element of dermographia is present or when the individual only gives minor or negative skin test responses. We have seen people "starved" and malnourished because of skin-test findings, in which clinical correlation had not been proven; and we have seen unsatisfactory results with attempts in hyposensitization when the total allergic load had not been considered to determine that fungi or house dust were additional factors requiring hyposensitization. We have some patients, who in addition to hyposensitization have to avoid specific foods during a specific pollen season. There are no "short-cuts" to doing a good job. It is only by doing a good history and physical examination and carefully correlating the results of good skin testing techniques that the best results can be obtained, realizing that positive skin tests do not necessarily indicate clinical hypersensitivity and negative skin tests do not always mean absence of clinical hypersensitivity.]

According to Hebald,[351] the allergens most commonly used in specific injection treatments are pollens; house dust; chicken, duck or goose feathers; dog, cat, rabbit, or horse danders; and the spores of molds. Dust is probably the most common specific agent causing allergic rhinitis and asthma. Hyposensitization is accomplished with either a stock mixture of dust or dust from the patient's home. While cottonseed and kapok-seed may cause acute sensitivities, specific injection treatment with extracts

of these seeds is dangerous. He feels rather that the articles containing these should be removed from the home. [We agree on the importance of removing the substances from the environment, but we also hyposensitize, when clinically indicated, for kapok, and also for cottonseed, but with great caution.]

Hebald states that specific injection therapy is unnecessary for foods except for cereals, such as wheat, rye, corn and rice which cause symptoms when inhaled by bakers and cooks. He also points out that persons who react by inhalation can usually eat cereals without trouble. He also states, "A patient with late season hay fever who reacts to ragweed pollen extract may also react to grasses or trees. However, if no symptoms occur during the spring or early seasons, no treatment should be given. That is, therapy should be given for symptoms, not for skin reactions." Also he states, "Patients able to take a large maximum dose usually are benefited most. However, many persons are very sensitive, and the largest tolerated dose will be smaller than the ones listed in the table." The precautions he emphasizes are, "(1) When an injection is delayed or missed, the dosage is reduced and then increased slowly. (2) When fresh extract is used, dosage is cut to one-half or one-third and then increased slowly. (3) In a pregnant patient, dosage is decreased and discontinued at the season's end. (4) Dosage increments are carefully made on hot days, since antigens probably are absorbed faster." He points out that systemic reactions must always be anticipated and usually occur within thirty minutes of the injections. First signs are itching of the palms of the hands or elsewhere on the body, sneezing, coughing, and facial redness. Urticaria, angioedema, or asthma may ensue. At the first sign of reaction a tourniquet should be applied above the injection site, and 0.4 cc of 1:1000 epinephrine given above the tourniquet or in the opposite arm. If improvement is not obvious in a few minutes, the procedure is repeated. The next dose of allergen should be one-quarter or less than the previous one. The maximum dose thereafter should be less than the dose that provoked the reaction.

[We agree with most of his statements and his fourth precaution is a new one to us but worth consideration. In pregnant patients we give a maintenance injection about once a month after the fourth month, but do not stop at the end of the season, since most of our patients receive therapy throughout the year. Regarding anticipation of systemic reactions, we detain all patients for about twenty minutes after their injection, by which time, if there is to be any serious consequences, they usually have a marked local reaction or else have started with other complaints which suggest that prophylactic treatment should be started. One of our patients refused to stay after the injections were given and failed to tell us that he had slight local reactions after injections. During one injection he developed an immediate systemic reaction. This emphasizes that while in general, if properly handled, these substances are safe, they are not so innocuous as to be used indiscriminately and without proper precautions. The practice of releasing the patient promptly after injections is to be condemned. The patient should be released by the doctor, not the nurse, and only when the doctor feels that it is safe to go.

[We likewise have found that those who can tolerate the largest dose are usually benefited the most, and that treatment given perennially in pollen-sensitive patients begets better results than can be obtained from the preseasonal method, and with a much smaller percentage of reactions.]

Frankland[352] did a controlled trial on patients with seasonal pollenosis

to compare results from preseasonal high and low dosage. All patients had seasonal hay fever with or without an associated seasonal asthma and had never received previous injections for allergy. Regarding asthma, on low dosages only four of twenty-three who had had previous asthma had good results, while seventeen of twenty-four hay-asthmatics had good results on the high dosage. He concludes the high dosage is the best method. In another paper,[353] he reported on the use of four different kinds of grass extracts used for hyposensitization, some of which were in combination. There were fifty patients in each of the four groups, and he could note no difference in the results from any of the four different types of pollen extracts. He averaged approximately 84 per cent good results in hay-asthmatics in all groups. However, patients were permitted to give their own injections as directed by Freeman. They kept daily records of their symptoms. If there were any reactions, they were advised to add 0.1 cc of adrenalin and precede the injection by an antihistamine. He concludes the higher the dose of extract reached, the better the results. [We believe it is bad technique to allow patients to give their own injections or their own adrenalin and antihistamine. If the patients must give their own injections, the dosage must be lowered if there are local reactions at the site of the injections.]

Keeney et al[354] used cortisone or ACTH while rapidly hyposensitizing sixty-six patients (eight with acquired and fifty-eight with inherited sensitivity). They do not believe the steroids alter the mechanisms of hyposensitization. It was impossible to tell whether the improvement was due to the steroids or whether improvement was due to the more rapid hyposensitization. [We have given many patients steroids while they still had symptoms, but have not tried rapid hyposensitization concurrently. His concept evolved from the use of steroids for rapidly desensitizing individuals to posterior pituitary substances, insulin, tetanus antitoxin, and toxoid. However, the type of antibody being neutralized by these substances is probably different from the antibodies produced in individuals with pollenosis. In these individuals we are trying to produce a type of "blocking" antibody which is non-precipitating. Presumably these are in the globulin fraction of the serum protein and the body requires a certain period of time to produce these after the appropriate stimulus. It is questionable whether the steroids are capable of increasing the rate of formation of antibodies. It is also questionable whether we should credit such improvement to a possible increase in rate of formation when we know that frequently the circle of symptoms can be interrupted by steroids alone, and for an undetermined and variable period of time. It is possible that the answer may lie in suitable titration tests. At present it is best to realize that a good period of time is necessary to reach high dosages, even though initially in the lower doses, more frequent injections can be given. Further reports on this technique as regards pollen extracts would be appreciated, although the method seems of value for desensitization in specific instances of sensitivities to insulins, toxoids, antitoxins, et cetera.]

An answer to a query[355] states:

"It is impossible to give definite figures as to the length of time required for desensitization. At least three major variables contribute to this uncertainty. The nature of the allergy is important. In an induced allergy (insulin, liver, et cetera) it may be possible to produce effective and lasting desensitization in weeks or months. In naturally acquired allergy it is a more laborious process. Here, too, it depends on the nature of the symptoms. For example, it is more difficult to

produce relief from the nasal than from the bronchial symptoms. The characteristic of the allergen and the degree of exposure to it are important factors. It is much easier to accomplish clinical desensitization against grass hay fever than against ragweed and more difficult against mold allergy. It is easier to desensitize against ragweed in Boston than in Indianapolis or Chicago [because of higher ragweed counts in the Midwest], and more difficult to desensitize against house dust in a furniture upholsterer than in a businessman. Perhaps the greatest variable is the patient himself. Desensitization depends on an active process of immunity production. Some have the ability to respond rapidly or not at all. In seasonal hay fever many patients obtain results the first season. Those who have two excellent seasons may go for one to several seasons without treatment and occasionally indefinitely. In nonseasonal cases, such as dust allergy, fair results may be obtained in months in many instances. When the results are good, the intervals are lengthened. If the patient gets along between long intervals, the injections may be discontinued altogether. This may take one year or several years, and the period of relief is also uncertain. In other words there is no set pattern. All one can say is that a year of treatment is likely to produce good results without any possibility of forecasting permanency."

[Another variable which may require further study occurs in individuals with defects in globulin formation such as the individual with agammaglobulinemia. It is possible such a person cannot be desensitized.]

We have been discussing hyposensitization by the injection method. Swineford et al[356] treated twenty-one patients with hay fever, eight of whom also had asthma, with aerosols of pollen extract. Excellent results were obtained in six of eleven cases in 1953. There was negligible relief in four cases and moderate relief in one. In 1954, eleven of fourteen patients obtained good to excellent relief. Three patients obtained excellent relief both years. When treatment was successful, relief was noticed by the fourth day. Seven were treated co-seasonally alone; four received both pre-seasonal and co-seasonal treatment. Mild transient nasal and bronchial reactions were observed twenty times; the bronchial reactions were noted usually when bronchitis was present. Only one severe reaction occurred. This followed an unintentional overdose. Seven of eight patients who had injection therapy in previous years preferred the aerosol treatment. Aerosol therapy can be done at home with a hand nebulizer after tolerance for the aerosol is established in the laboratory. [We have not tried this method and cannot give a critical comment. There are many questions, however, which will need to be answered. Will such a method be safe in all patients at all times? How can you regulate the dose in an exquisitely sensitive individual who starts out at the usual level but quickly reaches his level of tolerance? Will such an aerosol used in hay fever patients predispose the patient to an allergic response in the bronchioles? Can such people revert to hyposensitization by the injection method again without danger? We know that penicillin aerosols and troches can sensitize so that adverse manifestations occur with intramuscular injections.]

The results of studies on long-term hyposensitization in bronchial asthma by aerosols have been reported by Zerykier and Boruhow.[357] In 185 chronic asthmatic patients with sensitivity to pollen, fungi, and house dusts, hyposensitization was achieved with an aerosol. They received inhalations of the specific allergen extract, mixed with epinephrine ascorbate, at first twice daily and, later, according to the response to treatment, at longer intervals. The treatment was continued as long as the clinical condition required, but not longer than three months. At the end of the treatment, 124 patients could tolerate an allergen concentration 10,000 to 100,000 times as strong as that which precipitated the

attack before treatment, without any marked change in their vital capacity; thirty-seven could tolerate a concentration 100 to 1,000 times as strong as the initial one; and in twenty-four patients no objective changes were observed. All patients felt subjectively well during the whole treatment. Only four suffered from severe attacks during this time and in one status asthmaticus developed. The results of nearly three years of hyposensitization by aerosol are at least as satisfactory as those obtained earlier by other means, including use of cortisone and prednisone. During the treatment the patient does not have asthmatic attacks because of the admixture of the bronchodilator principle with allergen aerosol. By using this treatment, the usual way of life can be continued and the normal capacity of work maintained. The authors believe that by this method the allergen and the bronchodilating compound are conveyed into the deepest parts of the lungs and probably create a local immunity. [The transposition of these data on equal terms with the units used by the injection method of hyposensitization would be of help in evaluating the result on an equal basis. We shall probably hear more of this technique in the next few years and hope the final analysis is as optimistic as these earlier indications.]

Ruiz Moreno and Martorelli[358] attempted hyposensitization by the perlingual route of absorption because of difficulties in treating respiratory allergies by the usual injections. They believed the method was especially good in patients who could not avoid exposure to their allergens. There were no serious reactions. [This method will probably also see more clinical trials in the next few years. There will probably be a limitation on the extent to which this method can be used because of the probable enzymatic effect of the saliva on the allergens used.]

Lowell et al[359] gave intravenous extracts to six patients with allergic disease of the respiratory tract, five with hay fever and one with bronchial asthma. The patients were sensitive to the extracts both clinically and by skin tests. The amounts which were sufficient to evoke respiratory manifestations produced little apparent circulatory or cutaneous change. No changes were observed in the skin sensitivity or in the circulating skin-sensitizing antibody or complement. [We think the deliberate intravenous administration of allergens is extremely dangerous because of the possibility of anaphylactic shock. Years ago, one allergist read a paper in a similar vein, in which he used intravenous administration of allergens for the purpose of desensitization, and another author reported the use of intravenous allergens in order to study the blood sugars before, during and after the anaphylactic shock. The procedures were considered too dangerous and were probably never published.]

Brunn,[360] as a result of five pathogenetically identical cases with the deaths either being allergic or anaphylactic in nature, concluded that with bacterial vaccines, one should allow no more than five days between injections, and if a systemic reaction occurs, the injections should be stopped entirely. Two of the deaths were caused by bacterial vaccines with death occurring only after a rather long latent period. The other three deaths were not due to the bacterial vaccines and death occurred quickly, a few minutes to two and one-half hours after the injections of the antigens. He concludes that an intravenous injection is a technical error and desensitizing injections should only be given by a physician. "Rush" desensitization is hazardous, and if the "rush" method is necessary, the patient should be in bed or the hospital. If a systemic reaction is possible, the patient should be watched closely every minute. One must

differentiate between bacterial allergic conditions of spontaneous origin and induced bacterial anaphylactic reactions.

Unger[361] has a long article on hyposensitization in which he discusses the indications and mechanism. Then the technique is given in detail as regards pollen, fungi, other inhalants and food extracts. Pre-seasonal, co-seasonal and perennial methods are outlined. In summary he states:

(a) "Hyposensitization, less accurately called desensitization, should be tried in all patients who are allergic to substances which they cannot sufficiently avoid. Included are pollens, molds, smuts, various dusts, and animal derivatives. Physicians may also give injections of extracts of other inhalant materials and of egg and wheat.

(b) "The mechanism of hyposensitization is discussed but no adequate explanation is as yet available.

(c) "The technique is discussed, especially that for pollen extracts and the other important inhalants.

(d) "Results are usually good, and the patient is usually able to withstand ordinary amounts of his offending allergen or allergens. In pollen asthma results are usually excellent.

(e) "Failures are usually the result of the incorrect choice of extracts, dosages which are too weak or too strong, the use of deteriorated extracts, and especially to failure on the part of the patient to avoid his offending allergens to the best of his ability."

Halpern and Modot[362] cleared a patient with baker's asthma by desensitization with flour extract. Denis[363] says desensitization is indispensable in one of three asthmatic patients; he prefers poly-desensitization "because most asthmatic patients are or become sensitized to a variety of agents. This treatment gives a rapid and long-lasting cure in 80 per cent of the patients treated." [We agree with his suggestion to give mixtures of inhalant materials to which the patients are exposed and which give positive skin tests. We often give special mixtures which, for example, contain 50 per cent house dust extract and 50 per cent of a mixture of equal parts of extracts of dog, cat or horse dander, feathers, kapok, rabbit hair, phyrethum, et cetera.]

Ordman[364] says desensitization with food extracts is unsatisfactory. Oral desensitization is a lengthy procedure but is sometimes worth trying. Injections may be given subcutaneously or intracutaneously; the latter technique, he says, is less liable to cause severe reactions. Sterling[365] states that many allergic patients who would benefit from desensitization are made worse by overdosing and subsequent constitutional reactions. Desensitization with potent materials should be undertaken cautiously in highly sensitive persons, with frequent minute doses in dilutions as weak as 1:100,000 to 1:200,000 intradermally. Comeau[366] suggests that desensitization should be started before hospitalized patients leave the institution. In his experience the principal cause of failure is the patient's unwillingness to keep up the desensitizing injections.

VACCINE THERAPY

Autogenous vaccine therapy in "intrinsic" asthma is not entirely a nonspecific protein treatment, according to Bergquist.[367] He feels a certain specificity for staphylococci exists. A staphylococcus vaccine should yield better results than a polyvalent vaccine in which there are no staphylococci. There are seasonal variations in bacterial flora with respect to both streptococci and staphylococci in asthmatic patients. In healthy patients staphylococcus of the albus type predominates. In patients with

"intrinsic" asthma, the *Streptococcus viridans* is the predominant organism. He based his conclusions on work with fifty patients, ages forty-one to fifty, in whom the autogenous vaccine was good in 58 per cent of the patients over a twelve to eighteen-month period.

Tuft and Frank[368] began to give intracutaneous rather than subcutaneous injections of vaccine from bronchoscopically aspirated bronchial secretions of many asthmatics. By varying the concentration and keeping the doses small they were able to give 0.1 cc without too much discomfort. The series were given in the fall and winter months for six years in asthmatic children with history of repeated colds preceding attacks. In 125 clinic and private patients for a total of 2,036 injections, they believed that with intracutaneous injections there was a lower incidence of constitutional reactions and it was easier to regulate dosage. They believe that stock vaccines and other vaccines should be given intracutaneously.

Frankland et al,[369] using autogenous vaccine, followed two groups of patients. One group received no vaccine and the other received vaccine. More than half of both treated patients and untreated patients were improved. Their results were proportionately similar in those who were selected for injections but did not actually receive them.

Baird[370] says:

"In experiments on animals we inject a vaccine. The same material is used for reinjection. When it comes to the study of man we obtain cultures, grow them artificially, kill them by heat or chemicals, prepare the completed vaccine and use this for testing. Obviously this is not the same substance that was originally removed from its source in man. If we could produce a test material which is absolutely identical with the original, the results might be different. The recently developed method of sterilizing vaccines by grinding in a ball mill until each bacterium is broken up, without the use of heat or chemical preservative, should come nearer to producing the native substance. Even so, the vaccine has been grown on an artificial medium which in all probability has produced some change which might be detected by immunologic methods. The usual procedure is to 'grow' the bacteria on a culture medium. The actual bacteria used in the vaccine are the descendants, many generations later, of the original bacteria which were removed from the patient's body or its discharges."

While Baird does not suggest that so-called autogenous vaccines are not at times useful antigens in the hands of many workers, he would recommend to those who are pessimistic about their results that they try again with the dosage schedule of sensitized stock vaccines. His main objection to autogenous vaccines is that there has not been any conclusive proof, merely assumption, that they are better than the stock vaccines.

Spielman[371] presents several cogent arguments against the validity of the respiratory vaccines and/or filtrates used today in the treatment of infectious asthma and respiratory infections: (a) Washings used in the preparation of vaccines removed valuable surface antigens; (b) physical or chemical killing of the bacteria modifies or deteriorates antigens; (c) metabolic products in the filtrates of Gram-positive organism vaccines important in the treatment of bacterial allergy are discarded; and (d) as prepared today, the filtrates used contain culture medium contaminants and do not ordinarily contain intracellular constituents. With an acellular antigen complex containing all the intracellular and surface elements of the bacteria that are involved in immunization and sensitization processes, the author found that, with this complex derived either from stock or autogenous samples, immediate skin reactions were ob-

tained in a large percentage of his cases. He obtained a preponderance of good results with hyposensitization with the acellular antigen complex in contrast to the poor results with the usually employed vaccines. The antigen complex was standardized at 0.12 to 0.24 mg total nitrogen. The lower concentration was used in the treatment of asthmatics.

Shinefield[372] also used the autogenous acellular bacterial antigen complex in 110 children, of whom thirty-three were asthmatic. Of these, seventy had been unsuccessfully treated with the usual respiratory vaccines. His treatment consisted of subcutaneous injections, twice weekly for four weeks, then weekly for six weeks, then every two weeks for one month and then monthly as long as necessary. The dosage was gradually increased from 0.025 ml to 0.15 ml. The average maximum was 0.035 ml, and the average duration of treatment was 7.8 months. With this treatment, 73.6 per cent became symptom-free; 18.2 per cent were improved; and 8.2 per cent showed no improvement. Relief was often prompt and followed on the first or second injection. There were no constitutional reactions or other side effects.

Baldwin,[373] in discussing infectious factors in asthma, says that either stock or autogenous vaccines are most effective after removal of the infected focus. This removal can follow the judicious use of antibiotics orally or as irrigants of the nose and sinuses, and by such surgical procedures as antral exenteration, polypectomy and removal of tonsils and adenoids.

The reader is urged to restudy the earlier part of this article in which the relationship between bacteria and asthma has also been discussed.

SYMPTOMATIC THERAPY OF BRONCHIAL ASTHMA

The greatest advance in the last few years has undoubtedly been the introduction of ACTH, cortisone and hydrocortisone; but in the last two years, the latter two have been almost entirely replaced by the newer steroids, prednisone and prednisolone. As of today cortisone and hydrocortisone, while still used in other branches of medicine, have been dropped by almost everyone for the treatment of bronchial asthma, allergic rhinitis, hay fever, urticaria, et cetera. Bram Rose[46] correctly said, "Perhaps the greatest advance in the treatment of asthma, although not in the understanding of this disease, was the advent of the steroid hormone."

A. ACTH, Prednisone and Prednisolone

Beginning in early 1955, these new synthetic hormones were introduced, with almost uniformly good results. The literature on prednisone and prednisolone has increased by leaps and bounds and that on ACTH shows no signs of abating. We have been swamped by papers from all over the world and, because of lack of space have been forced to quote from only some of the articles. Our apologies go to the other authors, many of whom have written very well. The amazing feature of most of the articles, especially those which deal with asthma, has been the almost complete agreement that it is an exceptionally good agent in controlling symptoms.

Burrage et al[374] correctly state the case regarding these hormones. "All of these compounds will suppress the symptoms of allergic disease if employed in proper dosage. None of the agents, however, permanently alter the overall course of the allergic disorders. Repeatedly it has been demonstrated that symptoms recur with, or shortly after, withdrawal. These agents are but newer forms of symptomatic therapy."

In an answer regarding a woman with intractable asthma, in addition to commenting on the basic concepts, it was stated:[375] "In almost every asthmatic patient, relief occurs promptly if the patient is placed in a hospital room equipped with rubber bedding and all the necessary precautions against inhalation of house dust. In the hospital the intravenous drip can be started, each liter with 5 per cent glucose in water to contain 0.5 gram of aminophylline with or without the addition of 20 units of corticotropin. About 5 to 6 liters are usually necessary over a period of about forty-eight hours. When the drip is discontinued, intramuscular injections of corticotropin are substituted in decreasing amounts, later to be replaced by the oral use of steroids if asthma persists. This technique is usually very satisfactory." [This has been simply stated and its dramatic effect can only be appreciated by those who had to treat cases of status asthmaticus in the days before the steroids.]

Nicol and co-workers, of Britain,[376] believe that cortisone lowers the body defenses by depressing the phagocytic activity of the reticuloendothelial systems, as manifested by the total and differential leukocyte counts in the blood and the gamma globulin level in the serum. Siegel et al[377] determined the plasma 17-hydroxycorticosteroid concentrations, and found that in those children with moderate or severe asthma, levels were significantly higher than in asymptomatic or mild groups or in the control group. In children receiving variable amounts of prednisone or prednisolone, the levels were found to correlate directly with the amount of these steroids used, but they could find no critical hormone level at which the majority of patients became asymptomatic. Davies[378] found no relationship between the severity of symptoms and corticoid excretion, but his findings suggested that there may be adrenal hypofunction in some patients with severe asthma. DiRaimondo and Forsham[379] note "the hourly urinary excretion of 17-hydroxycorticoids is usually maximal between 8 and 10 A.M. and minimal from 12 midnight to 2 A.M. Plasma levels of free 17-hydroxycorticoids closely parallel urinary excretion curves. The one-half time secretion is four hours. The peak values for both at about 9 A.M. are two to three times greater than the minimal values close to 1 A.M." Sleep, visual impulses, or moderate food intake appear to have no effect on the adrenocortical secretory activity. It should be noted that a dose of hydrocortisone given at night will be twice as effective in suppressing adrenocortical activity as when given in the morning. The adrenals secrete 70 per cent of the daily excretion of cortisol under basal conditions between 12 midnight and 9 A.M.

Fredell et al[380] studied nineteen patients on long-term continuous therapy, thirteen to fifty months with cortisone, 50 to 100 mg per day, to see if the adrenal cortex would still respond to corticotropin and to see the effect of long-term cortisone on other physiologic functions. They found the more prolonged the treatment, the slower is the response. They urge that patients recently on steroid therapy, who sustain increased stress, need additional cortisone because of the inability of the suppressed adrenal cortex to respond quickly to corticotropin. Since even small doses of these hormones influence the central nervous system and delicate psychologic balances, Fox et al[381] recommend learning as much as possible about the patient's psychologic make-up and the personal situation before administering the drugs.

There is little or no insight yet into the mechanisms by which these hormones produce their effects and their site of action. It is postulated

by Beck[382] that there must be some fundamental action on cellular metabolism, which may lead to an alteration in the mechanism of response of the cells to the many unknown factors which lead to disease. The progression of the disease suggests that one deviates the disease but does not alter its basic course.

Roskam et al[383] found that if intensive, continous or prolonged salicylate therapy produced sufficient levels of salicylemia, usually there was a significant increase in the blood level of the 17-hydroxycorticosteroids. An 8-gram daily dose of salicylates produces an increase almost equalling that occasioned by the injection of 20 mg of delayed action corticotropin. Hoffer[384] emphasized that it is impossible to assay adrenocortical activity and reactivity by means of eosinophil counts unless the total diurnal rhythm is represented. The adrenocortical response test of Thorne would be of no value in an individual on ACTH for three years [385] but the actual output of corticosteroids, as measured by chemical determination, would be much more instructive.

Regarding possible complications of steroid therapy, Fentress et al[386] reported on eighteen arthritic patients, three of whom developed peptic ulcer, one with perforation (this last patient received 5 mg prednisone five times daily for about three months). Eisenstadt and Cohen[387] reported osteoporosis and compression fractures from prolonged therapy. The cases reported have been relatively few, and only one prior case involving a patient with bronchial asthma has been reported. They recommend periodic x-rays of the spine and urinary calcium excretion studies to recognize early calcium depletion and prevent fractures. Larsen[388] described cases of retinal and refraction changes that occurred during treatment with ACTH. He recommends that patients treated with ACTH should have regular ophthalmologic examinations at least until it is known how often eye changes occur during such treatment. Corticosteroids seem far less liable to cause changes in the retinal vessels. DiNardo[389] reported that eight cases of sensitization to ACTH occurred in a series of 200 patients. He emphasized the diagnostic significance of skin tests as well as the need for discontinuing ACTH as soon as sensitization symptoms develop.

[Other reports regarding the role of ACTH as an actual sensitizer are accumulating. We ourselves have recently had five cases in which systemic reactions have followed both the intravenous injections of ACTH and the intramuscular injection of ACTH-Gel. In one of these, death was very close. Skin tests were positive in two of these cases. A full report is being prepared. The reader is urged to be on the lookout for reactions to ACTH, and we would appreciate reports from others who have seen such cases.]

Henneman et al[390] found that nearly all of nineteen patients with bronchial asthma, in whom prolonged cortisone therapy was abruptly discontinued, developed headache, nausea, vomiting, restlessness and muscle and joint pain, within twenty-four hours. These symptoms subsided spontaneously after two to five days. The alarming clinical state of these patients was not associated with significant changes in vital signs or in the laboratory tests performed. The cause of these symptoms is not apparent. Savidge and Brockbank, England,[391] reported on two deaths which occurred in a group of thirteen patients treated for bronchial asthma with cortisone. Suppression was never fully achieved. The reason for the deaths was unknown but it was speculated that too low a dosage was used and possibly a type of anaphylaxis may have occurred.

Johnson and Davey[392] believe steroids may be used in the presence of tuberculosis if streptomycin is given concurrently as protection against deleterious effects. When given alone, the adrenal steroids may permit or even encourage the spread of infection. [We would not hesitate to give intravenous drip with ACTH in tuberculous patients with severe asthma.]

Hill[393] studied the growth patterns of forty-three allergic children (thirty-two with asthma) during cortisone administration, and concluded the retardation in growth in children, taking moderate or small amounts of cortisone, is not sufficient to warrant withholding the drug when it is needed. One report in Queries and Minor Notes[394] covers the side-effects of steroids in children. Resistance to infections is lowered; dermatological manifestations of certain diseases may be masked or disguised, and some diseases may even be aggravated. The function of the adrenal glands may be usurped to such a point they cannot resume their normal function for an indefinite period. In such cases corticotropin may logically be used at the end of prolonged steroid therapy, with gradually decreasing dosages. To these effects must be added "moon face," obesity and pigmentation.

Hedstrom,[395] Johnson,[396] and Lockey[397] each discussed the slow intravenous use of ACTH, with favorable comments. Johnson, however, feels that steroids have no place in the long-term control of asthmatics, in some severe attacks of asthma, or in those patients in whom the usual measures have proved effective. Lockey told of the good effects in forty-one hospitalized asthmatic patients. The intravenous drip is continued day and night, as per the technique advised by Goodall and Unger. He believes broadspectrum antibiotics should also be used in most cases.

Brockbank et al,[398] by the double blind technique, felt aerosol administration of hydrocortisone was less effective than a placebo in bronchial asthma. Williot and Cuche[399] and Foulds et al,[400] however, report favorable results from inhalation of hydrocortisone; Foulds et al obtained definite improvement in twelve of fifteen patients, with poor results from placebos. Increasing the dosage to over 15 mg did not increase good results. They feel that local treatment with hydrocortisone is valuable not only for asthma but also for allergic conjunctivitis and allergic rhinitis. In addition, there are no dangerous side effects as can occur with systemic steroid therapy.

Burrage and Irwin[401,402,403] state that in some cases of acute asthma hydrocortisone by vein works faster than ACTH. They also point out that hydrocortisone is not a magic drug, its action is slow, and one must not wait until all is lost. Older methods of treatment are to be tried first, but it is useful in status asthmaticus, initial therapy in intractable asthma, and, in major surgical procedures, for carrying through patients whose symptoms of asthma have been suppressed by long periods of administration of steroids. Grater[404] showed that four of six asthmatic patients responded to intravenous hydrocortisone in about five to six hours, and two responded favorably in forty-eight hours when oral cortisone was added.

Regarding a ten-year-old asthmatic boy who had had steroids for six years and the question of future therapy including ACTH (which he had never had), one consultant[405] answered:

"The problem as posed here is occurring with increasing frequency and underscores the advisability of not starting hormone treatment with chronic allergic

diseases. Not only is it exceedingly difficult to stop the use of such potent hormones, but such therapy of asthma and other allergic disturbances materially increases the difficulty in treating such hormone-treated patients. This is unfortunate, for there is as yet no adequate substitute for making a specific diagnosis in allergy and then either having the patient avoid the incriminated materials or treating him specifically. Substituting a maintenance dose of corticotropin for prednisolone should be tried in the hope that this might stimulate adrenal function. Sometimes the dosage of corticotropin may then be tapered off gradually after a few weeks. But if it becomes impossible to eliminate the use of the drug, as is often the case, then there is no alternative to attempting to make a specific diagnosis of allergy, even if this has to be done while the patient is receiving a maintenance dose of prednisolone, corticotropin or both. Sometimes hormone therapy cannot be eliminated until at least a part of the allergic load is detected and specific exposures are reduced."

The other consultant said:

"From the evidence at hand there would be no indication for either concomitant or intermittent administration of corticotropin. In these situations many allergists and pediatricians realize that a calculated risk must be taken, with the dangers of almost continuous asthma in a developing youngster weighed against those inherent in the prolonged intake of steroids. The present consensus is that clinical disuse atrophy is not averted by the administration of corticotropin and that small doses of prednisolone are well tolerated by these patients if certain safeguards are observed."

[One should add that this ten-year-old asthmatic boy was given only injections of autogenous vaccine prepared from his respiratory tract, and a "complete course of desensitization has been carried out, without benefit," according to the query. It is doubtful that any series of vaccine injections, however successful, constitutes "desensitization." Furthermore, in almost every youngster with asthma, positive skin tests for inhalant and/or food allergens can be obtained by careful scratch and/or intradermal tests, these to be followed by rigid avoidance of causative allergens and by hyposensitizing injections of those allergens which are inhaled. Good results are obtained in almost all cases; the prolonged use of steroids in a ten-year-old boy is very rarely necessary.]

Kennedy and Thursby-Pelham, England,[406] felt that, until more is known of the long-term effect of cortisone on the adrenals, the advisability of prolonged treatment with cortisone seems questionable. But they found that cortisone given orally in children did increase ventilatory function about 13 per cent; when epinephrine was inhaled, the combination led to an increase of 28 per cent. Schwartz[407] points out that the early use of corticosteroids, in conjunction with the antibiotics, for a period of two to seven days for asthmatic attacks ushered in by acute upper respiratory infection, may not only decrease the duration and severity of the attacks but may also prevent the development of status asthmaticus. DeCosta[408] points out, that with proper care, the administration of cortisone to a pregnant woman is not harmful to either mother or child. Hartling and Wegelius,[409] MacLaren and Frank,[410] Savidge and Brockbank,[411] Turiaf et al,[412] Walton,[413] Gregoire,[414] Wang et al,[415] and the subcommittee on Clinical Trials of Asthma of the Medical Research Committee, United Kingdom[416] all have favorable comments regarding the use of steroids and their long term use when proper precautions are used. Walton,[413] in his 153 asthmatics who were given cortisone and/or ACTH, had the following findings and results: 15 per cent were sensitive to aspirin. Of four patients with inactive tuberculosis before steroids, one became activated but, because of severe asthma, steroids had to be

continued, along with anti-tuberculosis therapy, with good success. Of three patients with peptic ulcer, one required subtotal gastrectomy, a second had severe bleeding with recovery. In eighteen patients who required major surgery, each was given 100 mg or more of cortisone intramuscularly just prior to and immediately after surgery; seventeen of the eighteen recovered uneventfully. Moon face occurred in some, and fifteen patients died during Walton's five-year period of therapy with these hormones.

Gregoire[414] also discusses patients with both bronchial asthma and pulmonary tuberculosis. In a series of eighteen patients with both conditions the asthma was so severe as to necessitate use of ACTH as well as anti-tuberculous therapy. In his twenty-year-old man who had tuberculosis for two years, with positive sputum and asthma since the age of three, the patient was given 20 units of ACTH intravenously and daily for five days, then intramuscularly daily for three weeks; then 10 units daily for one year; then five units daily. The sputum became negative and the general condition markedly improved, as confirmed by studies of his vital capacity, residual capacity and other tests. The author suggests that by markedly improving the patient's asthma, the ACTH may actually have helped to convert this patient's tuberculosis from an active to an inactive state.

Frank and MacLaren[417] studied seventy-two patients with chronic asthma, of whom thirty-two received cortisone; sixty-two hydrocortisone; and twenty-two received both in a separate series. No serious complications arose when adjuvants were given. Weight gain occurred in almost all. In another group without adjuvants three cases had exacerbations of their previous ulcer symptoms. They believe the usual maintenance dose in a chronic asthmatic is usually sufficiently low with hydrocortisone and the new steroids to obviate the use of any adjuvants; and if high doses are necessary, the accompanying dangers may be counterbalanced by proper adjuvant therapy. Thus it appears that for the chronic asthmatic who needs it, continuous therapy over several years is perfectly compatible with maintenance of normal health. Prednisone and prednisolone, however gave better results, with less side effects.

Grez et al,[418] in fifty-two asthmatic patients treated with ACTH and/or steroids, did bronchoscopic examinations, which in forty-five cases showed perfect correlation between the clinical improvement and the bronchoscopic and histologic changes. In six, there was discordance between the bronchoscopic and histologic improvement; in one there was no improvement.

Vallery-Radot et al[419] treated ninety-five patients with severe asthma with corticotropin, cortisone or hydrocortisone. Of the fifteen patients in whom therapy failed or proved unsatisfactory, four died. Necropsy showed the usual lesions of status asthmaticus. The long-term results were variable; only ten patients gained benefit from corticotherapy for more than six months. Prolonged treatment from two months to three years was practiced in sixteen patients and was successful in twelve of them. There were three complete failures and one fair result. There is no means of judging the individual patient's chances for successful treatment in advance, since the result seems to be independent of age, severity, or duration of disease, and whether the asthma stems from an allergy or a bronchial superinfection.

Rosa and his associates[420] studied the effect of corticotropin combined with a phosphate of polyphloretine. The effect of a dose of 20 I.U.

per day on ten patients with asthma lasted twenty-four to forty-eight hours. The effects of this new ACTH combination last four times longer than those of plain ACTH for beginning doses; they last eight times longer for maintenance doses. The combination was well tolerated and did not cause side effects.

Bonner and Homburger[421] reported that the action of ACTH is potentiated and prolonged when a zinc hydroxide suspension of the carboxymethylcellulose purified hormone is used. Smaller doses and fewer injections are required than with other forms of repository ACTH. Banghart and Watanabe,[422] in comparing ACTH gel with zinc ACTH, felt that two-thirds as much of the zinc preparation was needed as the gel and that duration of the zinc ACTH seemed longer than the gel. Also the zinc ACTH seemed to have less quantitative effect on serum electrolytes and less tendency to produce diabetes and gastric ulcers. Davies and Williams[423] were concerned chiefly with the results of short term therapy, presenting the effects of treating forty-four patients with chronic asthma and six with chronic bronchitis with fifty-seven and seven courses respectively, of cortisone, corticotropin gel and/or hydrocortisone. Eleven of the asthmatics were in status; the remaining thirty-three had intractable asthma. In the asthmatics 87.5 per cent of the courses gave good results. The temporary relief afforded lasted an average of thirty days but ranged from one day to 240 days. In these patients with severe asthma, continuation of hormonal therapy seemed desirable in from 40 to 50 per cent of the patients. The authors observed failure of response in a patient who had purulent sputum but also a marked drop in eosinophils. This patient's condition later improved in response to antibiotics and general measures. The hormones seem to relieve asthma due to nonpurulent obstruction of the bronchi but fail to relieve the obstruction due to a frankly purulent bronchitis.

Discretion in the use of ACTH and cortisone was urged by Unger and Unger.[424] These drugs afford symptomatic relief but are not curative. Careful allergy survey and adequate therapy based on this survey are stressed. The prompt use of ACTH and/or cortisone is urged in critical cases, e.g. severe serum sickness, severe asthma and exfoliative dermatitis. These hormones should also be used in those patients in whom the usual allergy management has failed. Of fifty patients with bronchial asthma results were excellent in sixteen, good in twenty-six, poor in eight. Symptoms recurred in twenty of seventy-seven patients when the hormones were stopped. Side effects included edema in six; peptic ulcer in two; the appearance of tubercle bacilli in the sputum in one.

Rosa and Bergami[425] favor a combination of corticotropin, ascorbic acid and adenosine triphosphoric acid. The mixture is named "Actavis" and is given slowly by the intravenous method. Improvement was obtained in sixteen of twenty patients with status asthmaticus. Anderson[426] also prefers the delayed action ACTH; hydrocortisone was superior to cortisone in thirteen of sixteen asthmatics. Baldwin and associates[427] had good results with both ACTH gel and cortisone; sixteen of his patients were operated on while on these hormones and there were no complications. Seven of his sixty asthmatic patients died but only two were taking hormones at the time of death.

Fyles, Pare and Rose[428] studied the effects of corticotropin and cortisone on respiratory functions. There was a rapid improvement in vital capacity, maximum breathing capacity, and the index of intrapulmonary mixing in seven of his eight asthmatic patients. One showed no changes,

and in three the residual volume remained elevated although the other changes were remedied by the hormones. Therefore, if therapy is sufficient to remove "bronchospasm," the pulmonary abnormalities can be reversible.

Serafini and DiNardo[429] make three interesting comments: (a) The newer prednisone is superior to the older cortisone; (b) if emphysema can be reversed, the patient is an asthmatic; and (c) six of his patients proved allergic to ACTH by developing asthma or anaphylactic shock. Therefore it is necessary to test for ACTH-sensitivity whenever treatment is repeated.

Rose et al,[430] in fifty-eight patients with acute asthma, state that the persistence of asthma is not associated with a rise in the level of glucocorticoid excretion in the urine. Spontaneous recovery from asthma and recovery induced by nonspecific therapy, however, are associated with a rise in this level. The results suggest that the asthmatic patient may excrete smaller quantities than do normal subjects, and that the persistence of asthma may be due in part to an inability of the pituitary or adrenal to augment the output of corticoids or to respond to the stimulus of asthma.

Bruce Pearson[431] obtained good results in almost all of seventy-eight patients who received ACTH and/or cortisone while ambulant or hospitalized; there were three deaths in this series. Lipman[432] also did well with most of his four hundred and seventeen allergic patients who received steroids over a three-year period. Good results were obtained in 67.6 per cent, fair in another 18.9 per cent, and no benefit in 13.5 per cent. Side effects occurred in thirty-six cases (8 per cent), with recovery in all on cessation of therapy. There were no deaths.

In a series of 200 children, mostly asthmatic, Levin[433] also found ACTH and steroids very useful. He found no allergic reactions to these hormones. From Moscow, Kogan[434] reports that short-term results in asthmatics given ACTH were very good in eleven of twenty-six patients, good in five, fair in three, poor in three, and nil in three. In patients with pulmonary fibrosis and intractable asthma with chronic pulmonary insufficiency but without true bronchial asthma, injections of ACTH had no effect.

Maxwell from Australia[435] states that the intelligent use of ACTH and the adrenocortical steroids "has done much to save lives of patients in status asthmaticus and to relieve the unbearable dyspnea of intractable asthma, but it must be remembered that while these therapeutic measures may control they do not in virtue of their own action cure the asthma from which the patient suffers. Nevertheless, such control is of great importance as it may enable the patient's general health to so improve that he may develop an immunity to the causative factors and thus be restored to normal health." In patients who are on prolonged prednisolone therapy, he injects 40 units of ACTH-Gel daily for seven days "to stimulate the adrenal cortex which probably will have undergone some degree of atrophy during the treatment with prednisolone. The prednisolone administration is then resumed." Romansky[436] also has a good article regarding the concomitant use of antibiotics and steroids.

PREDNISONE AND PREDNISOLONE

In 1955, extensive clinical trials with the analogs of cortisone and hydrocortisone, *prednisone* and *prednisolone*, respectively, showed that these compounds have between three and four times the potency of

cortisone or hydrocortisone, with much less salt-retaining effect, according to Hollander.[437]

"Atopic asthma (bronchial asthma) has often been a therapeutic problem with cortisone therapy because the salt retention and edema at times increased bronchial edema as well. Observations reported at the International Conference on Prednisone and Prednisolone indicated that prednisone was far superior to previously available steroids in treating asthma. Of fifteen asthmatic patients, eight had formerly been unsatisfactorily controlled despite administration of large doses of cortisone, hydrocortisone or corticotropin. Fourteen of the fifteen were well controlled with administration of 15 to 25 mg of prednisone per day in divided doses. Several other series of cases of asthma treated with prednisone and prednisolone showed similar responses."

To emphasize these similar responses, the next forty or so references enumerate the authors who felt their results with prednisone and prednisolone in the treatment of bronchial asthma were worth reporting. Arbesman and Ehrenreich[438] felt both were especially good because of the absence of sodium retention and potassium depletion. In their 101 cases with asthma or rhinitis, gastrointestinal symptoms developed in nineteen patients. Jenkins,[439] in a study of thirteen patients who had side reactions, especially edema, and who had no reactions and did very well with prednisone (Meticorten®), concluded that, while prednisone is potent and very helpful, one must continue good anti-allergy treatment and watch for possible reactions. Johnston and Cazort[440] treated more than 200 patients with various allergies with prednisolone. The effect was more prompt and more effective, and with a lower incidence of side reactions than with the earlier steroids. In only two patients did the medication have to be stopped. Siegel and associates[441] treated sixteen children with 5 mg of prednisone three or four times a day. Most showed some rounding of the face, but these new steroids were very effective not only for asthma but also for atopic eczema. Kahrs of Norway,[442] in a study of six patients with severe asthma, found prednisone the best means available today. Küchmeister et al[443] (Germany) reported on the use of prednisone in thirty-seven patients, five of whom were asthmatic. During the last three days of prednisone therapy he adds 20 to 30 units of repository corticotropin daily. Muller (Germany)[444] believes the lack of water and salt retention makes prednisone more suitable than cortisone for therapy in cardiac, hypertensive and elderly patients. Pestel (France)[445] has a good general paper on the new steroids and likes the greater dietary freedom for the patient. He believes it is advisable to administer anabolic steroids in association, especially when massive doses are being used. Estrogens and testosterone can prevent depletion of calcium or phosphorus. Schwartz[446] presented a patient with diabetes mellitus and asthma previously treated with high doses of adrenalin and cortisone to the point where he was on 150 to 200 units of insulin a day. On prednisone, after initial high doses, his insulin requirements dropped to 35 units. Scimone et al (Italy)[447] found prednisone excellent in long term therapy because it is almost lacking in harmful side effects. Bollet, Black and Bunim[448] discussed the major undesirable side effects resulting from these analogues. Apparently gastrointestinal complications in the form of ulcer or bleeding were the main ones, occurring in three of their eighteen patients, as shown by x-rays. They suggest that aluminum hydroxide gel be given routinely to patients taking these medications. One case of severe depressive psychosis developed. Their cases were rheumatoid arthritics. Serafini

and his associates (Italy)[449] treated twelve asthmatic patients with prednisone, with a partial or total remission in most. A slight increase in body weight was noted in three patients, and acne pustulosa and a slight moon-shaped face in one. Sheldon, McLean and Matthews[450] used prednisone successfully in fifty-one patients with severe asthma. Eleven of these obtained relief even though previous therapy with 75-200 mg. cortisone daily had failed. Prednisolone was equally effective when substituted. Skaggs et al[451] reported on eight asthmatic patients, and also were impressed by the absence of salt retention and edema. Solem and Römcke (Norway)[452] also obtained good results with these steroids in three asthmatics.

Taub, Kaplan and Aaronson[453] tell about their results with 107 adults and forty-four children and two infants with severe bronchial asthma. Twenty-three of the 153 patients were hospitalized for status asthmaticus, initially treated with corticotropin and maintained thereafter on prednisone.

"The usual regimen consisted of an initial dose of 30 mg of prednisone divided into six equal doses of 5 mg for from twenty-four to forty-eight hours. After this a therapeutic period of three to seven days was started with doses averaging from 20 to 30 mg per day. The patients were then placed on maintenance therapy with 5 to 15 mg of the drug per twenty-four hours which was continued for weeks or months.

"An improved emotional state varying from a feeling of well-being and cheerfulness to one of euphoria was the first symptom noted in the hospitalized patient receiving prednisone. In the next twenty-four to forty-eight hours the degree of wheezing, cough, dyspnea and expectoration decreased; the sputum of some patients became thin and clear, as compared to the thick, tenacious and mucoid material that had been produced previously. In the next period the appetite improved and the ability to sleep and rest was noted. With the continued use of prednisone the need for additional drugs diminished, and many patients received only maintenance therapy with prednisone. The same degree of improvement as in the hospitalized group prevailed in the patients with acute and chronic asthma, except that in the chronic group the need for additional drugs remained more or less constant because of long-standing complications and sequelae. Twenty-nine of the eighty-one patients with acute asthma obtained complete relief, forty-nine had partial relief, and three were therapeutic failures. Fourteen of the forty-nine patients with chronic asthma were completely relieved, thirty-one partially relieved, and four were failures. The side effects that were previously noted with corticotropin, cortisone, and hydrocortisone occurred to a greater or lesser degree with prednisone, but the dose required to produce these effects (more than 30 mg per day) was proportionately larger and the length of time was much longer.

"Attention is called to the serious complications of adrenal insufficiency after stress phenomena and to the value of long acting corticotropin to correct or offset this complication. The use of antibiotics in selected patients in whom an infectious component was suspected increased the effectiveness of prednisone or corticotropin in these patients."

Other good papers on this subject have been written by many, including Turiaf, Marland, Jeanjean (France);[454] Vallory-Radot (France),[455] who advises that patients on prolonged treatment with prednisone should receive two injections every two to three weeks of ACTH-gel to prevent aplasia of the suprarenal cortex; and Villa and Ballabio (Italy).[456] The Committee for New Drugs Research Council, American Academy of Allergy,[457] confirmed the good results; noted the side effects, especially reactivation of peptic ulcer; found little or no difference between prednisone and prednisolone; and advised that in hay fever only severe cases should receive steroids. Members of the Panel Discussion on Prednisone and Prednisolone, 12th Annual Meeting of the American Academy of Allergy[458] also agreed there was little to choose between

prednisone and prednisolone. Similar good results have been reported by a consultant;[459] by Arnoldsson (Sweden);[460] and by Andersson (Denmark).[461]

Barach, Bickerman and Beck[462] discussed clinical and physiological studies with Metacortandracin® (prednisone). They gave 40 to 80 mg daily to thirty patients with severe chronic bronchial asthma, gradually reducing to a maintenance dose of 30 to 40 mg per day. The new drug gave much quicker relief than the older steroids, with subjective relief in twenty-four to forty-eight hours in twenty-five of these patients; seventeen obtained complete remissions; the only failure occurred in a man who was addicted to Demerol. Pulmonary function tests were also improved, with a mean per cent increase in vital capacity of 53.2 per cent, in the fast expiratory volume of 63.6 per cent; and in the maximum breathing capacity (eight patients) of 44.5 per cent. Abdominal distress occurred in three patients.

De Gennes and Mathieu de Fossey[463] found prednisone does not cause retention of either sodium or water; patients do not need a low-sodium diet. The drug increases the amount of hydrochloric acid in the gastric juice more than does hydrocortisone, but it has little effect on gastric juice volume and none on uro-pepsin secretion. Prednisone can replace cortisone and hydrocortisone except in the treatment of adrenal cortical hypofunction.

In Bickel's thirteen patients, including three with bronchial asthma, gastralgia occurred in four and a sudden bout of hematemesis in another.[464] Bickerman et al[465] found prednisone valuable in fifty patients with pulmonary emphysema and pulmonary fibrosis, with increased exercise tolerance in 86 per cent. Other good papers come from Capuani,[466] Criep,[467] and DaCosta.[468]

In a study on the comparative effects of prednisone and cortisone, Demartini and associates[469] conclude:

"Prednisone has the following biological properties: (1) effective anti-inflammatory and antirheumatic properties demonstrated in humans and rats; (2) interference with glucose utilization; (3) ability to suppress elaboration of 17-hydroxycorticoids by the adrenal cortex following intravenous administration of corticotropin; and (4) anti-inflammatory property is quantitatively, milligram for milligram, greater than cortisone, thereby permitting less sodium and water retention, and potassium diuresis at dosages needed for symptom control in rheumatoid arthritis. We believe that qualitatively the mechanism of its anti-inflammatory and antirheumatic action is similar to cortisone and that prednisone is preferable to cortisone as an anti-inflammatory agent."

Feinberg and Feinberg,[470] in eighty allergy patients of whom fifty were chronic asthmatics, also obtained good results with doses of prednisone which were about one-fifth those of cortisone: their maintenance dose was about 10 to 15 mg per day, although asthma plus infection usually called for larger doses. Thirteen of their patients felt that prednisone, irrespective of the dose, was more effective and less disturbing than cortisone. Other articles have come from Schwartz,[471] and Spies et al,[472] and Vallery-Radot et al.[473]

Arbesman and Ehrenreich[474] found that 9 alpha fluorohydrocortisone, though very effective for sodium retention and reduction of eosinophils, did not relieve asthma, whereas Meticorten did bring prompt relief in their fifteen asthmatics. Grater,[475] using the "double-blind" technique found that fluorohydrocortisone (F-Cortef®) and prednisolone (Delta-Cortef®), instilled in the nostrils and conjunctival sacs and hydrocorti-

sone hemi-succinate (Solu-Cortef®), nebulized into the lungs of patients with moderate asthma, all showed definite objective and subjective improvement in most of the patients; but no effect from systemic absorption could be detected.

[From this long and time-consuming review and from our own experiences, everyone must conclude that the introduction of prednisone and prednisolone has added a glorious chapter to the spectacular advances we have all noted in the field of allergy, especially bronchial asthma. We would not like to return to the days when these two were not available. Many of our more severe asthmatics are no longer pulmonary cripples. Some of these do not now need these steroids; others do, and all of us must keep them up in such cases, but at a minimum dosage level and with due regard to complications. We ourselves give injections of ACTH-Gel at intervals, these depending on the dosage of the prednisone; others do not believe these injections necessary. We are chiefly worried about gastric complications and we keep asking our patients regarding epigastric burning. Perhaps, as one author suggested, periodic roentgen search for peptic ulcer should be made.]

OTHER SYMPTOMATIC THERAPY

Bernstein and Klotz[476] emphasize that the treatment of patients with bronchial asthma ultimately depends on its cause. In their article they point out that "emergency treatment is usually directed at relieving only a symptom, and the prime requisite of immediate therapy is the prompt and safe procurement of an adequate airway. Epinephrine is still the drug of choice for prompt relief. Aminophylline is dependable for bronchial relaxation, and potassium iodide is a time-proved remedy when expectant, liquifying action is required. Oxygen may be needed temporarily. The use of morphine is still prohibited, and meperidine (Demerol®) hydrochloride is to be used rarely. Safe sedatives are of great value. Corticotropin and cortisone represent important additions in the treatment of patients with allergies, and particularly in status asthmaticus, with pitfalls that must constantly be kept in mind." The authors also point out that psychogenic and infectious factors must also be overcome. "Thorough medical and allergic investigations must be made. The best treatment for patients with bronchial asthma is prevention, by treating the precursor state before asthma occurs."

Blanton[477] has an interesting approach. The asthmatic who coughs himself out of an attack is best treated with epinephrine and iodides; the asthmatic who coughs himself into an attack, possibly infectious, is best treated with codeine. Bullen[478] emphasizes that the asthmatic patient should be educated to treat his attack promptly. Many do not because of the erroneous idea that adrenalin may damage the heart or therapy may lose its efficacy if used too often. Immediate treatment shortens an attack and lessens the amount of medication needed. Whittenberger[479] states that as in most diseases the importance of psychologic factors should not be underestimated. Strong motivation is effective compensation for even severe physical handicaps in respiratory function. Confidence in the physician and the power of suggestion can benefit the patient when medications and physical therapy are of no objectively determinable merit. This fact makes difficult the evaluation of a therapeutic agent or method.

Prickman[480] has an excellent article which approaches the general treatment differently than the usual papers. This paper should be read

by all who are interested in helping the asthmatic patient. On smoke he says, "No patient with asthma should smoke—anything, at any time, in any amount. I know of no smoke which is completely benign." His explanation on cough is well worth quoting in its entirety. "Time is well spent in explaining to the patient the usefulness of mucus and the mechanism of its formation. He should be told that mucus is normal; that it protects its parent surfaces against respiratory irritants; that it is an ointment for inflamed bronchial and tracheal membranes. Mucus, therefore, should be left in place to perform its functions. If even physicians forget these things, so much more do patients forget them and need to be reminded that the more mucus they cough up, the more will be secreted; the membranes will not be left long without a protective coating.

"It means a great deal to the patient to be told that any excess secretions are slowly raised by means of cilia and other mechanisms until they reach almost to the top of the trachea. At that point the presence of the excess mucus excites a tickling or other sensation. This is a signal to the patient to open his mouth and very gently to clear his throat. This will expel excess secretions that have not been allowed to become thickened and tenacious. To keep the secretions thin, the patient's tissue must contain an adequate quantity of water. A good rule for him to follow is to drink the equivalent of a glass of water each waking hour. Iodides, ammonium chloride, or other expectorants are entirely ineffectual if the patient is dehydrated. The patient who is being instructed in prophylactic measures should be impressed with the need to treat his air passages as gently as he would his eye. Once informed of the dangers of overcoughing, the patient's reaction commonly is, 'Why wasn't I told not to cough so hard? I've been doing just the opposite of what I should be doing for years.'" [Fortunately, not too many asthmatic patients are afflicted with a bad cough. But, unfortunately, we frequently forget this simple phase in discussing the disease with the patient, thus we neglect the patient who does have a severe cough but accepts it as part of the asthmatic picture, and frequently fails to query the doctor about it.]

Other good general papers were by Krantz on the use of drugs in bronchial asthma;[481] Holler;[482] Carryer;[483] Wright;[484] Farmer;[485] Gaarenstroom;[486] Feinberg and Feinberg;[487] Ehrlich, Faber and Goodman;[488] Dur;[489] Davis;[490] and the section on bronchial asthma by Criep[491] in "Current Therapy."

B. Sympathomimetic Drugs

Bullen[478] emphasizes that in an acute attack of asthma, edema of the bronchial mucosa, which narrows the lumina of the bronchi, is the initial stage in the production of dyspnea. The dilatation and increased permeability of small blood vessels that lead to edema are apparently, at least in part, the consequence of histamine release and are best counteracted by administration of epinephrine since epinephrine is the most potent antagonist of histamine. Epinephrine and related drugs cause constriction of the blood vessels, relieving edema, and also relax smooth muscle. Antihistamines are not as effective as epinephrine in combating histamine release, perhaps because the amount of histamine released is greater than that which can be combated by the dose of antihistamine the patient is able to tolerate.

Bullen believes that a nebulizer with 1:100 epinephrine should always

be at hand, and the patient or some member of the family should be able to give subcutaneous epinephrine in order to abort attacks early. [We desire to have our patients in such control that they do not have to have the crutch of having the nebulizer always at hand. It is difficult to tell in advance which patients are psychologically disposed to use the nebulizer in anticipation of an attack rather than early in an attack. Patients who use a nebulizer many times a day in anticipation are difficult to wean off such apparatus. We rarely permit injections of epinephrine by the family or by the patient. Admittedly there are situations where this practice might be tolerated, but we prefer the doctor to give the epinephrine because he is thus in close contact with the patient. If frequent injections are necessary, the patient should be hospitalized and then steps should be taken from the allergic point of view. The use of epinephrine and other similar drugs should be only a temporary expedient for relief until specific measures can be undertaken. If such is not done, then one is only treating the symptom and not the disease.]

Blumenthal, Brown, and Campbell[492] state:

"It is evident from animal and clinical work that the action of epinephrine is definitely correlated with the pH of the blood. Epinephrine fastness seems due, at least in great part, to either general or local acidosis. By elevating the pH to the alkaline side, correction of the condition often results,—with dramatic relief of epinephrine resistant asthmatic states.

"Increasing the dose of epinephrine beyond that usually given, especially if other therapeutic measures are used, may give good response. However, molar sodium lactate, unless contraindicated because of the danger of sodium retention, is the treatment of choice. In these cases, endogenous epinephrine apparently gives results either because of increased sensitivity in alkaline media or because of depressed effects of acetylcholine in increased blood pH."

[This is a logical approach and somewhat similar to the question as to why larger doses of insulin are needed in diabetic acidosis. However, the above theory cannot explain why the usual epinephrine-fast patient will often respond to epinephrine given intravenously.]

Refsum[493] worked with continuous intravenous administration of epinephrine in severe attacks of asthma, pointing out the advantages of the immediate effect, stability of effect, and the ease of rapid regulation. He uses 5 mg of l-adrenalin in 500 ml 5 per cent glucose solution. This amounts to 10 μg of adrenalin ml, which he usually gives at the rate of 5 μg/minute initially. By regulating to control the symptoms the rate is usually 5 to 15 μg of adrenaline/minute. This is adjusted downward to the minimum amount necessary to yield satisfactory results. [In some of our cases we use this method concurrently with aminophylline in patients who cannot take steroids; and even in patients who are taking steroids but not responding well enough we may add a cc of epinephrine hydrochloride, 1:1000, aqueous, to the liter containing the ACTH for the infusion.] Gaksør[494] also reported on the intravenous use of epinephrine. He added heparin to his infusion. Jagic[495] suggested epinephrine in suppositories.

Freedman,[496] London, reported that overdosage with adrenalin may cause death within minutes. A 4 mg dose given subcutaneously may be fatal; 8 mg is probably the largest tolerated dose. One of his recommended precautions is that the concentration of adrenalin solutions for spray inhalation should be as low as compatible with therapeutic effect, and should never exceed 4 mg per cubic centimeter (0.4 per cent). Piperoxan should be injected as soon as possible after an overdose of adrenalin.

For an adult, 15 mg of piperoxan should be given intravenously; if 20 mg or more of adrenalin has been given, 30 mg of piperoxan is recommended. Speed is essential. Piperoxan produces few side effects; since duration of action is brief, prolonged hypotension does not occur. [Adrenalin overdosage occasionally happens when patients give their own injections; severe shock can occur when the injection is accidentally given in a vein. As regards inhalation of epinephrine almost all the inhalant solutions on the market are 1 per cent or 1:100; some of the "patent" preparations are even stronger. We doubt that 0.4 per cent solutions, as advocated by Freedman, can be nearly as helpful to the patient as the 1 per cent.]

Bronkephrine® is discussed thoroughly by Foland.[497] Bronkephrine® is ethylnorepinephrine, 1-(3, 4-dihydroxyphenyl) -2-amino-1-butanol hydrochloride, a compound with chemical properties quite similar to those of epinephrine but which differs in several important respects. The lack of pressor action is the most notable difference, along with a general lack of excitation so often encountered with epinephrine. Foland states that the degree of bronchodilatation produced by Bronkephrine is as good as that produced by epinephrine, although on a weight basis a higher dosage is required. He feels that he has seen tolerance develop far less frequently and to a lesser degree with Bronkephrine, and, therefore, Foland now uses Bronkephrine for his asthmatics to the complete exclusion of epinephrine. [As with the numerous digitalis preparations, each doctor should use the drug with which he is most adept. In the past two years tolerance to epinephrine has, in our experience, been rare. This may be due to the introduction of the newer steroids or to better general care of the individual patient. When we have patients with severe asthma, which would include those who have used the nebulizers frequently, we hospitalize them, where, with appropriate treatment, they usually clear within a few days. During their stay in the hospital we advise the family to take steps to make the home as allergen-free as possible, and as a consequence these patients rarely have to return to using the adrenalin, at least for many days to months. Perhaps the development of fastness to adrenalin can be correlated with inefficient management of the allergic patient.]

An answer to a query[498] states:

"There is no chemical incompatibility between epinephrine solution and repository corticotropin injection. However, there are at least two objections for this combined form of therapy. The added solution of epinephrine dilutes the repository corticotropin injections so that the effect of prolonged absorption from the latter may be disturbed. Epinephrine is designed for the immediate relief of the asthma, corticotropin for the more remote effect. Both drugs could be given at the same time (but not in the same syringe) only if the effect of each is required."

Itken and associates[499] obtained favorable results with a new drug, an N-substituted arterenol derivative (code name JB 251, Lakeside Laboratories). After a year's study they conclude that the drug gives temporary relief to patients with bronchial asthma. It can be given orally or can be nebulized. There were no serious effects in 126 patients; it was effective in 111; the mist (1:200 solution) was useful in thirteen patients who were not relieved by 5 mg oral doses; orally, ninety-three of 126 obtained at least partial relief. In a double blindfold study, using thirty-four patients, the inhalation of 1:200 solution of this JB 251 was as effective as epinephrine 1:100, and was better in that reactions

were much less. Four mg tablets of JB 251 were more effective than 50 mg ephedrine and appear to be useful in some patients who do not respond to ephedrine.

OTHER BRONCHODILATOR DRUGS

Emphasis has been placed upon the use of pulmonary function tests before and after medications in order to study comparative results. Snider et al[500] found that while this is an ideal approach, some patients could not perform the maximum breathing and one second vital capacity tests because of severe asthma. Proper evaluation of bronchodilator drugs should include both tests. Samter and De Rango[501] feel the same way about determining the efficacy of symptomatic medications. Cander and Camore,[502] by using the ventilation tests, found a new bronchodilator agent, 5 per cent Dapanone,® to be about as effective as 0.5 per cent Isuprel®, when both were used as aerosols. Maximum benefits were obtained by the simultaneous use of these nebulized drugs and intravenously-given aminophylline. Their data showed variability in the vital capacity and maximal expiratory flow rate in asthmatic patients without therapy, and re-emphasized the need for careful control studies in the evaluation of bronchodilator drugs. There were no systemic effects noted following use of Isuprel and only one slight headache with Dapanone. But twelve of the sixteen patients who were given aminophylline had systemic reactions consisting of flushing of the face, vertigo, weakness, nervousness, tremors, nausea and vomiting, after the aerosal was used ten minutes. [The question is whether the reaction was due to the aerosols or the aminophylline or both. They gave 0.5 gram of aminophylline in ten minutes which would make us suspicious that it was the aminophylline which was the main initiating factor for the adverse effects. It would have been of interest if they had used only 0.24 gram of aminophylline]. Dapanone is 3,4-dihydroxyisopropylamine propiophenone hydrobromide.

Salomon, Herschfus and Segal[503] used aerosols of epoxytropine tropate methylbromide, the anticholinergic drug Pamine®, and found it as effective as Isuprel in increasing vital capacity and maximum breathing capacity in patients with chronic bronchial asthma. But they found that the hand nebulizer failed to give adequate relief in those with moderate or severe symptoms. Frank and associates[504] also found Prantal® about as good as epinephrine and Isuprel. They gave this new drug orally and subcutaneously.

Spielman[505] did work with a dual action pill. The tablet had an outer coating which contained 10 mg Isuprel and an inner core which contained 30 mg benzyl-ephedrine, 8 mg Luminal®, and 120 mg theophylline. In fifteen patients, in whom each had two or more severe attacks, twelve patients obtained marked relief in five minutes. Eight of these were completely relieved after twenty minutes. There were also ten other patients with chronic asthma who were given tablets each day. Four of these were maintained on this method for one month. Nine of the ten obtained satisfactory relief, four of whom were adrenalin-fast. The average twenty-four hour dose for good results in chronic asthma was two to three tablets. [It seems as though with this type of tablet as with the aerosols, everyone is hunting for the magic panacea which will "cure" asthma. The idea of maintaining these individuals on symptomatic therapy such as this by necessity will occur, but it is not without danger and should

constantly be discouraged because of the false sense of security it gives to the patient and frequently to the doctor. They are necessary, however, for some patients during the initial phases of hyposensitization and at times when a well-managed patient's tolerance is exceeded. Also there is a tempting thought in the idea of taking only one pill instead of several. However, the disadvantage persists as with any combined medication, and that is, it is difficult to increase a specific type of drug without increasing the others. Another danger inherent in such combination tablets is that some doctors do not evaluate the ingredients, but think only of the immediate and prolonged effect. In some patients the barbiturate can be a factor of a sensitivity reaction and in others a factor of addiction. We do not like to use barbiturates as a general rule but tend to utilize an antihistamine, e.g. diphenhydramine when sedation is desired.]

Schiller and Lowell[506] compared the effects of SC4959 (1-n-propyl-3-ethyl-5-chloro-6-aminotetrahydropyimidinedione), Hvadrine® (diphenhydramine, aminophylline and racephedrine) and a placebo, and felt the Hyadrine® was very effective with clear cut advantages over either the placebo or SC4959. The SC4959 was only slightly effective. Feinberg and Feinberg[507] pointed out that ephedrine may produce over-stimulation of the central nervous system and difficulties in urination in men past middle age. Racephedrine may be tolerated when ephedrine is not. If neither is tolerated, propadrine is worth trying. [The urinary retention from ephedrine can sometimes be more of a problem than the asthma and can occur in some men before middle age, now that middle age is later in life than it used to be. We like the mixtures which contain a sympathomimetic drug, an antihistamine and some with theophylline. Some of these come in liquid form and are useful in children with nocturnal attacks.]

Digilio and Munch[508] studied the effect of large inhalation doses of levo- or racemic epinephrine in 102 individuals, who suffered from various cardiac diseases, diabetes, and hyperthyroidism, all of which conditions are considered as being adversely affected by epinephrine. The average dose for the treatment of bronchial asthma is four inhalations. For this study the authors wished to give a larger quantity and therefore adopted a standard dose of forty-eight inhalations. An occasional patient received ninety-six inhalations. These massive doses produced no appreciable change in the electrocardiograms, blood pressure readings, pulse rates, or blood sugar levels in any of the patients of this series. [We have not found adverse affects when medication is judiciously used. We have seen asthmatics with elevated blood pressure which falls when he is relieved of his asthma, but we usually use smaller doses of epinephrine and repeat as necessary. In such cases we avoid long-continued epinephrine (as in oil or as Sus-Phrine®). A diabetic will not eat much during a severe episode of asthma, so it is encouraging to know that such treatment will not have any direct effect on his blood sugar other than making it possible for him to eat. Aerosols, however, will not reach the affected areas unless the air passage is open; in a severe asthmatic attack the simplest method is usually by needle.]

Prigal[509] points out that particles for aerosol must be small (0.5 to 3.0 microns); the apparatus must be adequate to deliver enough particles, and the material must not be too concentrated nor too cold. Aerosols have either a local or systemic effect or both. He is fond of aerosol therapy and uses bronchodilators, including sympathomimetics and amino-

phylline; also he uses inhalant antibiotics and mucolytics, e.g. Triton A 20, trypsin and Dornase. Denton[510] uses a Mist-O_2-Gen nebulizer, and points out that asthmatic patients may use the nebulizer in conjunction with an intermittent positive-pressure breathing apparatus. Miller et al[511] treated twenty-two patients with pulmonary emphysema, of whom eleven had chronic asthma. These were given oxygen by intermittent positive pressure four times daily for two weeks, with no improvement, and three of the patients seemed worse. In this same group, however, inhalation of Isuprel with or without the oxygen was of distinct though temporary benefit in about 75 per cent of the cases.

C. Xanthines and Related Drugs

In the use of the xanthine derivatives there were two main developments. One was the criticism of aminophylline's toxic effects and the other was the development of choline theophyllinate.

Nolke's article[512] received publicity in *Time* magazine. He reported on ten children with asthma and three with other respiratory disorders who were treated with aminophylline suppositories. The first case was a little girl, two and one-half years old, who was given 3¾ grains of aminophylline in a suppository without relief. This was repeated in four hours. Continuous projectile vomiting occurred subsequently. Upon transfer to another hospital and proper intravenous fluids the child recovered. A boy, aged three and one-half years, received the same type of suppository every six hours. He showed toxic effects after the sixth suppository, and developed convulsions after the twelfth, with subsequent death. Case three was a seven-month-old boy who received four suppositories in twenty-four hours and almost died. Nolke gives a good analysis of the cases with his only main criticism being that the rectal suppository is a poor means of theophylline or aminophylline administration. He believes the unpredictability of absorption makes a fixed therapeutic regimen dangerous. [Our main criticism is that aminophylline is seldom necessary in children. Epinephrine and potassium iodide are the drugs of choice. Adults will inform the doctor when they are nauseated from too much aminophylline, but children can only vomit and show other toxic effects. Aminophylline in water is easily instilled into the rectum in both children and adults, with dosages up to 10 grains in adults, and 5 grains or less in children. One such instillation in twenty-four hours seems sufficient. Aminophylline suppositories are also an excellent form of medication if given every twelve to twenty-four hours, and are usually very safe.]

White and Daeschner[513] recommended 3.5 mg aminophylline per kilogram of body weight for intravenous or intramuscular administration. 5 mg per kilogram for oral administration and 7 mg for rectal administration. Dosage should not be repeated oftener than every six hours. The toxicity of aminophylline is potentiated by small doses of ephedrine. Main symptoms are excitation, irritability, vomiting, muscle twitching, pallor; hematemesis occurs frequently, and massive gastrointestinal hemorrhage may be fatal. Love and Corrado[514] report four cases with symptoms from overdosage; and Veum and Schwartz[515] suggest that the proper rectal dose for a child less than three years old weighing about 30 pounds is 100 mg. Therapeutic accidents are due to the false assumption, from the labeling as half-strength, that the product is suitable for pediatric use.

Batterman et al,[516] Brown and Clancy,[517] Katz and Mast,[518] and

Simon[519] all have favorable comments on a new preparation, choline theophyllinate (Choledyl®). Oxtriphylline (choline theophyllinate) has been described by the Council on Pharmacy and Chemistry[520] thus:

"Oxtriphylline is a theophylline compound that produces the mild diuretic, myocardial stimulating, vasodilator and bronchodilator actions of similar xanthine derivatives. Oxtriphylline is more soluble than aminophylline; it also appears to be more stable, is better absorbed from the gastrointestinal tract and produces less gastric irritation. Thus it is tolerated orally in larger doses and produces higher theophylline blood levels than can be achieved with equal doses of aminophylline. Hence, in contrast to theophylline and the theophylline compounds which are poorly tolerated by the stomach, oxtriphylline can be administered orally in doses adequate for the management of bronchial asthma (including pulmonary emphysema) and for the control of paroxysmal cardiac dyspnea and Cheyne-Stokes respiration. [Is the mechanism of action the same in all these diseases?] Oxtriphylline is essentially nontoxic at clinically effective dosage levels. It is administered orally. In the treatment of asthma, dosage for adults may range from 0.1 to 0.4 gram four times daily. The recommended initial dosage is 0.2 gram. Two weeks or more may elapse before the full effect develops. The usual dosage for children six years of age or older is 0.1 gram three or four times daily; the drug is not recommended for younger children."

[In selected patients only we have tried doses of 0.6 gram four times daily initially and in other patients only 0.1 gram is tolerated. In general, we have found we can use higher doses proportionately of oxtriphylline than of aminophylline, and with less gastrointestinal reaction. Aminophylline in combination with sympathomimetic drugs also works well. We have not tried such a combination with oxtriphylline, although we would suspect equally good results. This type of medication should be advantageous in asthmatics whose symptoms are aggravated by cold air, if given approximately twenty to thirty minutes before they are exposed to the cold air; patients with angina are often helped by nitrates taken before they indulge in activities which would precipitate an attack of angina.]

We have no personal experience with the use of aminophylline in aerosol but it has been used by some, and recently advocated by Adelkamp.[521]

D. Antihistamines

In general, antihistamines have not been of much value in asthmatics except as they act as sedatives, and when used their drying qualities must be considered. Antihistaminics are not considered by Brown[522] to have been successful in treating bronchial asthma, but when taken early these drugs have aborted mild asthmatic attacks in some patients. Antihistaminics in combination with ephedrine may elicit a better response than when the bronchodilator drug is used alone.

Walker[523] postulates that a natural human antibody, an antihistamine, is produced in the blood stream when histamine is injected, thus reducing the allergic state of the individual and gradually changing an allergic person into a nonallergic one. By using histamine as a therapeutic agent in asthmatics who had failed with previous therapy, she obtained marked improvement for periods varying from six months to six years in 55 per cent of asthmatics without emphysema, in 45 per cent of chronic asthmatics with emphysema, and in 60 per cent of cases with seasonal hay fever treated during the season only. [This report is interesting and the study should be checked to see if other workers can also obtain such good results by injecting histamine itself. Actually, histamine has been used for years in the treatment of various allergic diseases; the con-

sensus of opinion to date has been that it is of little benefit except perhaps in urticaria and serum sickness. Histamine, unless given in minute dosage, aggravates asthma.]

Dramamine®: Garcia Hernandez[524] (Cuba), using 1 to 2 cc of Dramamine, obtained good results in overcoming the crises in bronchial asthma. He treated fifty-eight patients. Intravenous Dramamine was also used in some cases in solutions of 1 cc Dramamine to 10 cc of a 5 per cent glucose solution or 2 cc of Dramamine in 500 cc of a 5 per cent dextrose solution administered at the rate of 25 drops per minute.

Dibistine®: In a study of 204 adults and eighty children, eighteen of whom were asthmatics, Rubin[525] reported the results of using Dibistine, a combination of Pyribenzamine® and Antistine®. Of the eighteen with chronic bronchial asthma, four had good results, three fair results, and eleven poor results.

Diphenylpyraline: This new antihistaminic was reported as being of no benefit in six asthmatics,[526] but Nachtigall,[527] in his series of 121 allergic patients, secured moderate to excellent relief in four of nine asthmatics.

Clistine Maleate®: Carbinoxamine maleate was reported by Garat et al[528] as producing inconstant and variable results in bronchial asthma. Their series included only three cases of bronchial asthma.

Buclizine®: 1-p-chlorobenzhydryl-4-p-tertiary butyl benzylpiperazine dihydrochloride is discussed by several authors. Blatt[529] used this drug in treating sixteen asthmatics. with results excellent in six, fair in seven, and poor in three. The outstanding feature was the almost complete absence of side reactions. Gaillard[530] obtained excellent results in three of six patients with bronchial asthma. Landau and Gay[531] found that a single dose of Buclizine protected guinea pigs against the effects of histamine and prevented anaphylactic reactions from aerosolized antigens for one to three weeks. Schiller and Lowell[532] tried the drug in seventy patients with perennial allergic rhinitis and urticaria, but not in asthma.

Sandostene®: 1-methyl-4-amino-N′-phenyl-N′-(2′-thenyl)-piperidine tartrate, was used in 124 patients by Clein,[533] and was only given to those whose symptoms were not relieved by the grass pollen antigens and other treatment. In the twelve cases with hay fever and asthma, two had excellent results, seven good results, and three had no results. The author was impressed with the lack of undesirable side effects. He also felt that, since this drug is available in tablet form, in syrup, and in ampules, the form most suitable for each patient can be chosen. The combination with calcium results in a potentiation of the effect on cellular and vascular permeability. There was no drowsiness. [In our experience, limited to intravenous therapy, drowsiness did occur.]

Plimasin®: This combination contains 25 mg tripelennamine hydrochloride and 5 mg methylphenidylacetate. The former is Pyribenzamine, an antihistamine, and the latter is Ritalin® which is a mild analeptic and cerebral stimulant, with action lying between that of caffeine and amphetamine, to counteract the sedative effect of the antihistamine, Steinberg[534] tried it in eighty-five allergic patients, including two asthmatics. He recommends it for those who require an antihistamine and who must remain alert, as in driving cars, et cetera.

Dutton and Halpin[535] seem to disagree regarding results from a new antihistamine designated FC-1 (Schenley Corporation). Halpin reports it to be good in eighty-one patients with symptoms due to molds and ragweed but "in no instance were asthmatic symptoms appreciably relieved nor

reduced in severity, with FC-1. Similar findings have been our experience with other drugs of this nature (antihistamines)." Dutton, however, used the same drug in forty-nine allergic patients and obtained good results in 60 per cent of all types, with failures in 17 per cent. He reports success in patients with both pollen hay fever and pollen asthma. [This disagreement might be due to the enormous amounts of pollen to which Halpin's patients are exposed (Cedar Rapids, Iowa), and the much less exposure in El Paso, Texas, Dutton's home.]

Jimenez Diaz and associates[536] were not able to demonstrate significant variations in the quantity of histamine eliminated in the urine of asthmatic patients. In some cases histamine in the blood was increased during an attack. Histamine in the stools, however, was remarkably increased in asthmatics. Their studies did not support the theory of defective destruction of histamine in bronchial asthma, but the asthmatic is very sensitive to histamine.

[Antihistamines play a limited role in the treatment of patients with bronchial asthma. If one remembers that there are at least four different groups of antihistamines, frequently it will be found that a patient can be aided by one from another group if the first one does not help. There has been no dramatic contribution in 1955 and 1956 in the field of antihistamine therapy, but at least there have been some new ones reported which may help an individual patient, if antihistamines are warranted. At the present stage there is no one antihistamine which is best in all patients, but there are many to try if one does not seem to help.]

E. Miscellaneous

Rooks et al[537] found that *mechanical filters* and *air conditioners* provide symptomatic relief in hay fever but are less effective in controlling airborne fungus spores. Mechanical filters remove about 97 per cent of ragweed pollen, 53 to 91 per cent of Hormodendrum spores, and 88 to 92 per cent of Alternaria spores from the air. Air conditioners circulating indoor air reduce ragweed pollen counts by about 94 to 98 per cent and spore counts by 86 to 94 per cent. Efficiency of air conditioners is decreased when outdoor air is circulated.

There were two answers in Queries and Minor Notes[538] on this subject which will be quoted.

> "Many tests have been run with room air conditioners. Three general types are available, a room window filter, a combined filter with cooler, and the precipitator or the combined filter-precipitator type. All of them remove pollen from the air to a greater or lesser extent, the precipitator type being the most efficient. The question of effectiveness is relative. Patients with hay fever whose symptoms improve when exposed to half normal amount of pollen will improve with the least efficient of the filters. Those who are extremely sensitive may respond only to the most efficient apparatus. The relief will also depend on the habits of the individual and on the amount of time spent in the conditioned room. Those who have pollen asthma do not have as good a response as those who have nasal symptoms only."
>
> "Conventional room air conditioners, equipped with fibrous filters will remove only the larger pollens from the air. Special cloth filters or electronic precipitators must be used to remove all but the smallest pollens for the treatment of pollen asthma. Millipore filters will remove all pollens, but require too much power to force the air through."

An electrostatic precipitator combined with an air conditioner, according to Novery et al,[539] is designed to remove particles 0.1 micron in diameter from the air presented to the unit. The machine did remove all the ragweed pollen from the air presented to it, but when two grams

of ragweed pollen were dispersed in a room, more than a week was necessary to remove it from the room, including the floor, furniture, etc. The combination with an air conditioner unit resulted in comfortable temperature in all equipped rooms even in hot weather. Patients with ragweed hay fever began to improve within one hour after entering a room with the equipment. Those with asthma did not do as well. The machine is effective and comfortable for ordinary clinical use.

Two other queries regarding air filters for asthmatics[540,541] both emphasized such filtration is effective for hay fever but not for asthma, and much depends on the time such patients are in such an environment. The electrostatic precipitator is most efficient, but an air conditioner is often more comfortable.

[There are many things to consider and each step taken to improve the environment is of help. These machines are not cheap. If an individual is exposed for twelve hours to the pollens outside, it may take longer than twelve hours to get over the effects of the exposure regardless of which type of filter is used. Some asthmatics with superimposed infection cannot tolerate air-conditioning. In fact, such incompatibility suggests the presence of active infection which may need vigorous treatment. We cannot comment on which is the best filter, but if air-conditioning is desired and is tolerated it is not discouraged. One man with severe bronchial asthma due to ragweed, who built his house around an air conditioner and an electrostatic precipitator, stated he did well if he stayed in the house continuously, which was impossible for the whole season. By the following year his level of hyposensitization was at high enough levels so that he was not even aware the ragweed season had begun, and required no additional medication. It was his first year to be free of ragweed bronchial asthma in seven years, and he had practically no symptoms even when he was away from his home.]

There have been a few articles regarding the use of the tranquilizers in bronchial asthma. Ende[542] injected Chlorpromazine® intramuscularly into twelve patients with severe bronchial asthma. There was some improvement within one hour in eleven of the twelve. In some, the improvement was marked and in one it was life-saving. The only untoward side effect was a minor ulceration at the site of the inoculation. He felt the drug might be of value in alleviating the anxiety reaction associated with the attacks. In all instances the patients became sleepy and definitely more relaxed after the injection but wheezing was unchanged. Moyer et al[543] used the drug in a woman who, in the second trimester of her pregnancy, experienced attacks of status asthmaticus which yielded only slowly to the standard treatments. An injection of 50 mg of Thorazine® terminated the attacks within thirty minutes on three different occasions. Masbernard[544] tried the drug in nine patients and concluded that "provided that the dosage is strictly suited and very prudently reduced, eminent and lasting improvements are obtained without help of any other antiasthmatic." In status asthmaticus[545] 25 mg of Thorazine® should be given intramuscularly with the patient lying down and remaining so for at least one-half hour. The initial dose may be repeated after one hour, if the attack is not controlled and if no hypotensive effects occur. Oral administration of 25 mg or more every four hours can be substituted when the attack has abated. In cases where rapid control is not necessary, oral administration may be started at 25 mg two or three times a day and gradually increased if necessary.

Bendlowski[546] found methylpentyrol useful in alleviating the night

attacks of bronchial asthma in fourteen of fifteen cases. This drug is a non-barbiturate hypnotic. Gallini[547] (Italy) reported on a method of using sleep therapy in status asthmaticus. Sleep was induced slowly with amytal and was maintained for eighteen to twenty hours each day. The patients were studied for about three weeks, but the actual treatment lasted only fourteen to fifteen days because it took two to three days to induce sleep and five to six days to interrupt it gradually. The treatment brought about a quick and marked arrest of the status asthmaticus and a temporary disappearance of the asthma. In the five patients the results obtained were qualitatively comparable to those that are generally brought about by cortisone and corticotropin in patients with asthma. In these patients results were more remarkable because the hormone therapy had failed. Asher[548] says that the eczema-asthma syndrome of childhood is especially amenable to hypnosis. [As is obvious, there is still no panacea. Many forms of treatment may have many applications. We have recently tried tranquilizers, but have not had to use Thorazine, sleep therapy or hypnosis, and cannot fairly criticize these individual reports, but we wonder what will be the final place of such therapy in the treatment of bronchial asthma, other than the relationship to concurrent anxiety states.]

We recommend aspirin and whiskey at bedtime in some asthmatics, so it was of interest to see a report on the sedative action of liquors.

"The sedative action of an alcoholic beverage[549] does not depend on the flavor of the drink, but on the amount of alcohol consumed. Although the sedative effect of alcohol somewhat resembles the action of barbiturates and when both are consumed a definite synergistic effect occurs, it would be a mistake to consider their effects to be identical. Measurable effects of alcohol occur when the alcohol in two ordinary drinks (about 30 grams of absolute alcohol) has accumulated in the body of an average-sized (150 pounds or 68 kg) individual. The chief objective symptoms would then be measurable loss of judgment and deterioration of vision. Barbiturates produce their threshold effects of moderate narcosis with about 30 mg. The ratio of the weight of alcohol to the weight of barbiturates for threshold effects would then be about 1,000 to 1. When fatal dosages of alcohol and barbiturates are compared, this ratio is about 100 to 1."

Sigal and Attinger[550] are favorably impressed by the use of Reserpine® as an adjunct in the treatment of bronchial asthma and pulmonary emphysema.

Howell[551] points out the value of bronchoscopy in the treatment of six patients with "asthma," especially in those who have symptoms which are not entirely explained by allergy. In these patients mechanical factors may be discovered which may account for the poor response to therapy. One individual had an atelectasis; one had bronchiectasis; one had stones in the main bronchi; one had an enlarged thyroid; and one had a generalized inflammation of the entire left bronchial tree. [This approach cannot be too strongly emphasized. Idealistically, each asthmatic patient should be bronchoscoped as part of a complete evaluation but this is not always practical nor truly necessary. Bronchoscopy, however, is frequently forgotten, yet can be truly life-saving in some cases.] Israels et al[552] also discuss bronchoscopy in asthma. Their bronchographic pictures are very good, and they describe anomalies in asthmatic patients. The reader is urged to read this article and study the pictures.

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(To be concluded in November-December issue)

STUDY OF ANAPHYLAXIS

The study of anaphylaxis has become more and more extensive since Richet's original observations on Actiniae. The difficulties surrounding the question are great. A few have been overcome, but a large number still remain. No theory of anaphylaxis will explain all the facts, any more than any theory will entirely explain immunity in general. Indeed, anaphylaxis is so intimately connected with the general problem of immunity that a solution of the former would probably go far towards explaining the latter. The general trend of immunological research at the present day appears to be along the lines of physical chemistry, more especially as it relates to the chemistry of the colloids. Hitherto this has been the "No Man's Land" between the physicist and the biochemist on the one hand and the bacteriologist on the other, and it may be that further exploration of this little-known territory will add greatly to our knowledge of those problems which are so intimately connected with immunity and infective disease.—Dr. A. Besredka, Anaphylaxis and Anti-Anaphylaxis and their Experimental Foundations. (1919)

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

PSYCHIATRIC ORIENTATION OF GENERAL PHYSICIANS

Ten years ago the American College of Allergists held the first organized meeting to determine what role the allergist should play in the psychotherapy of allergic patients. As a result of this meeting a Committee on Psychosomatic Allergy was appointed and it has functioned since.

The ANNALS OF ALLERGY is glad to report that in a dispatch from Washington by the World Wide Medical News Service, the American Psychiatric Association has formally acknowledged that physicians other than psychiatrists should be encouraged to treat many emotionally disturbed patients. The report by the World Wide Medical News Service is as follows:

PSYCHIATRISTS, GP's LAUNCH PROGRAM TO IMPROVE PHYSICIANS' ORIENTATION

(By World Wide Medical News Service, Washington Bureau)

A 10-point program, designed to increase the psychiatric orientation of general physicians and thereby encourage them to treat many emotionally disturbed patients they now refer to state mental hospitals, has been launched by the American Psychiatric Association.

To co-ordinate the program, the A.P.A. has established the General Practitioner Education Project, with five representatives of the A.P.A. and five from the American Academy of General Practice forming the liaison advisory committee.

The director of the project is Dr. Charles E. Goshen, of the A.P.A. staff, working with Dr. Daniel Blain, medical director of A.P.A. It will operate under a one-year grant of $27,500 from the Lasker Foundation. As outlined by the liaison committee, these are the basic objectives:

1. Strengthening the medical school curriculum in the field of social psychiatry to cover more adequately the common emotional disorders encountered by the general physician.
2. Channeling more information from A.P.A. on "changing attitudes" toward the use of tranquilizing drugs.
3. Forming organized educational programs in social psychiatry so that the general physician can assume a "proper role" in the community.
4. Providing a period of psychiatric training in internships, where possible.
5. Establishing preceptorships for general physicians in general psychiatry.
6. Providing mental health fellowships for general physicians to provide three months of intensive training in established psychiatric centers.
7. Developing refresher courses in psychiatry for general physicians on a regional basis.
8. Increasing use of general physicians in state mental hospitals, with organized didactic training.
9. Extending use of general physicians on a part-time basis in community health clinics under supervision of experienced psychiatrists.
10. Encouraging more contributions to current general medical literature by qualified psychiatrists.

Dr. Goshen said, "Our program is actually a reflection of the fact that the general physician in any given community is usually the first to see—and often the only one to see—an emotionally disturbed patient."

He also said that many general physicians need greater psychiatric orientation in determining which patients should be referred to a psychiatrist and which can be handled satisfactorily by the general physician; in the proper use of tranquilizers; in the mechanics of referral in mental cases; and in more effective techniques for handling marginal emotional upsets.

The Editorial Board of the ANNALS OF ALLERGY is glad to see that the pioneering effort of The American College of Allergists is now extended by organized psychiatry itself. We shall look forward to seeing the results of this study by the American Psychiatric Association.

CONTRAINDICATIONS AND INDICATIONS

The National Analysts recently interviewed 191 people for the American College of Apothecaries with the purpose of measuring consumer understanding of printed labels. It comes as no surprise that half of the consumers, when asked what a patient should try to discover about a medicine before deciding to use it, said that they were interested chiefly in the indications for taking the drug, and only a slightly lesser number in the dose required. The contents of the medicine interested 30 per cent of those interviewed, and the possible harmfulness, only 37 per cent. A mere 14 per cent mentioned permissible frequency of use. Only 3 per cent brought up the subject of cautions or warnings.

When asked what information they thought a label should give, 76 per cent wanted dosage and direction, 50 per cent the name of the product and the name of the manufacturer, 50 per cent the contents, 43 per cent the indications and 39 per cent cautions or warnings.

Of laxatives, 11 per cent took doses in excess of those specified, while of cough and cold remedies, 16 per cent took doses above those suggested, with 20 per cent ingesting excessive doses of headache and pain-killing remedies.

The analysis concludes by saying that the interest of the consumers wanes after they have read the indications and the directions, but that they are much more "careful in their use of prescription medicine."

It is traditional for a patient to be given medications with only the doses and the directions for taking them and nothing more. If the findings of National Analysts are correct and their work is confirmed, physicians ought, perhaps, to reverse their normal procedure and discuss the contraindications first and the dose and indications last. How many overdosages (and allergic reactions) due to repeated self-medication would this procedure avoid?

Papers of Interest

Jackson, G. L., and Smith, D. A.: Analgesic properties of mixtures of chlorpromazine with morphine and meperidine. Ann. Int. Med., 45:640 (Oct.) 1956.

Ingestion of chlorpromazine increased the analgesic response of 25 mg of meperidine (Demerol) to that of 75 mg.

Jordan, W. S., Jr.: Human nasal cells in continuous culture. I. Establishment of two lines of epithelial-like cells. Proc. Soc. Exper. Biol. Med., 92:867 (Aug.-Sept.) 1956.

Epithelial-like cells derived from normal nasal mucous membrane have been sub-cultured successfully fifty times over a period of one year.

Cooperberg, A. A., and Eidlow, S.: Haemolytic anaemia, jaundice and diabetes mellitus following chlorpromazine therapy. Canad. M. A. J., 75:746 (Nov. 1) 1956.

The three disorders, which occurred within a few weeks after chlorpromazine treatment had been stopped, spontaneously cleared in three months.

Lipman, W. H.: Allergic reaction to the Salk poliomyelitis vaccine. GP, 15:94-98 (Feb.) 1957.

Reactions to Salk vaccine such as coryza, cough, local redness and generalized urticaria were noted in 304 of 3,970 first injections and 186 of 1,294 second injections. The incidence was reduced from 2.51 to 1.09 per cent when an antihistaminic agent was simultaneously injected.

Tuft, H. S.: The development and management of intractable asthma of childhood. Am. J. Dis. Child., 93:251-254 (March) 1957.

Report on 500 children aged five to sixteen admitted to the Jewish National Home in Denver. More than half were free of asthma within a few days following admission, and 30 per cent had less asthma during the first year. In some, the condition recurred during the respective pollen seasons. Discusses causes and types of treatment.

Correspondence. Untoward reaction to Equanil (Miltown). New York J. Med., 57:1969 (June 1) 1957.

Tachycardia, severe anxiety and fear and a sudden pruritic vascular flush occurred in two patients following the ingestion of Equanil.

Allanby, K. D.: Deaths associated with steroid-hormone therapy. Lancet, 2:1104 (June 1) 1957.

Eighteen fatalities supposedly due to steroid-hormone therapy are listed, with seven ascribed to infection, three to gastrointestinal hemorrhage, and three to perforation. The treatment is considered directly responsible for eleven of the deaths and as contributory in three. In four others, steroid hormones although administered are not directly implicated.

Zeligman, I.: Experimental contact dermatitis. II. Contact dermatitis in guinea-pigs induced by paraphenylenediamine and related compounds. J. Invest. Dermat., 28:121 (Feb.) 1957.

Since paraphenylenediamine is not a primary irritant, it is said to be ideal for the study of experimentally induced dermatitis.

Huebner, R. J.: Implications of recent viral studies. Pub. Health Rep., 72:377 (May) 1957.

Implies that many acute and chronic human disorders assumed to be noninfectious in origin may actually be caused by viruses discoverable by modern techniques.

Hounie, P.: Chronic sinusitis and the antibiotics. A.M.A. Arch. Otolaryng., 65:539 (May) 1957.

A report of the treatment of twenty-eight patients with subacute or chronic sinusitis by antral puncture, lavage and instillations of chloramphenicol or streptomycin "in obstinate cases.

Kautz, H. D.: Trends in drug therapy. J. Am. Geriatrics Soc., 5:122 (Feb.) 1957.

Review of drugs used in allergy. Also discusses antimicrobial, antineoplastic, gastrointestinal and immunologic agents, hypnotics, sedatives and hormones.

Raskin, N.: Agranulocytosis in patients treated with Thorazine—report of a fatal case. Am. J. Psychiat., 113:991 (May) 1957.

Another warning that patients require supervision.

Challenge for antibiotics. Chem. Eng. News., 35:22 (Apr. 22) 1957.

New synthetic drugs, the hexahydropyridamines, are effective against many Gram-positive and Gram-negative bacteria and some fungi.

PAPERS OF INTEREST

Fisk, A. A.: Anaphylactoid reaction to nitrofurantoin. New England J. Med., 256:1054 (May 30) 1957.

A case of anaphylactoid reaction with dyspnea, cold sweaty extremities, hypopiesia and low back pain due to nitrofurantoin is described.

Ionannidis, A. H., and Murdoch, J. McC.: Chloramphenicol in treatment of acute respiratory infection. Brit. M. J., 1:1157 (May 18) 1957.

Eighty patients with acute respiratory infections were given 2 gm daily for five days. Clinical improvement was noted in seventy-seven. Mild side-effects were seen in five.

Kies, M. W.; Goldstein, N. P.; Murphy, J. B.; Roboz, E., and Alvord, E. C.: Occurrence of lipemia in experimental allergic encephalomyelitis. Neurology, 7:175 (Mar.) 1957.

Lipemia is one of the characteristics of experimental allergic encephalomyelitis of guinea pigs.

McIntire, F. C.; Richards, R. K., and Roth, L. W.: Histamine release inhibition *in vitro* and antianaphylactic effects *in vivo* of some chemical compounds. Brit. J. Pharmacol., 12:39 (Mar.) 1957.

Screening of 2,500 compounds uncovered three which protected against aerosolized antigens. The nine best failed to protect against intravenous antigens.

Dowling, U. J.: Treatment and prevention of serum sickness. Indust. Med., 26:282 (June) 1957.

Long-acting chlorprophenpyridamine maleate is reported as effective in preventing serum sickness caused by antitetanus serum.

Dixon, F. J.; Roberts, J. C., and Weigle, W. O.: Direct and indirect effects of x-radiation on antibody-producing cells. J. Exper. Med., 105:417 (May 1) 1957.

Antibody responses may be inhibited by either direct injury to lymphoid tissue or by radiation effects on antibody-producing tissues.

Talbot, J. R.: Infective sensitivity and hypertension; a report of 36 cases. Wisconsin M. J., 56:246 (May) 1957.

A study of thirty-six patients is said to have shown that the "successful management of infective sensitivity seems to have a salubrious effect on associated hypertensive vascular disease."

Raskin, N.: Agranulocytosis in patients treated with Thorazine. Report of a fatal case. Am. J. Psychiat., 113:991-992 (May) 1957.

Of 625 patients treated with various amounts of Thorazine, three developed agranulocytosis. Two patients recovered, the third died. It is concluded that the dosage does not have to be high to produce agranulocytosis and that although Thorazine has been withdrawn and replaced by energetic treatment and the agranulocytosis is hematologically resolved, the patient may die.

Betetto, D., and Graziani, M.: The importance of the intradermal reaction to penicillin as an index of sensitization (In Italian). Gior. veneto sc. med., 11:149-159 (May-June) 1956.

The cutaneous reaction was studied in 150 patients treated with penicillin. Twenty patients (13%) were found to be sensitive. A positive Prausnitz-Kustner reaction occurred in 4 patients.

Farber, S. M.; Wilson, R. H. L., and Grimes, O. F.: Clinical evaluation of enzymatic therapy in diseases of the chest. Am. J. Med., 22:930 (June) 1957.

Serious side reactions are noted and caution emphasized.

Sternberg, L.: Antigen-antihistamine mixtures in the treatment of highly sensitive pollen patients. New York J. Med., 57:2069 (June 15) 1957.

Mixture not recommended.

Kwart, H., and Shashoua, V. E.: The structure and constitution of mucus. Tr. New York Acad. Sc., Series II, Vol. 19 (May) 1957.

A fascinating paper.

Chirico, A.-M.; Carfagno, S.; and Lytel, F.: Agranulocytosis after promazine therapy. New England J. Med., 256:899-900 (May 9) 1957.

Toxic effect of promazine, with recovery, has not previously been reported. Treatment consisted of penicillin, tetracycline and cortisone administration.

Smith, F. P., and Cleve, E. A.: Infections complicating cortisone therapy. New England J. Med., 256:104-108 (Jan. 17) 1957.

Three of six infected patients died following cortisone administration for rheumatoid arthritis in one, for rheumatic fever in the second, and for acquired hemolytic anemia in the third. The hazards of cortisone therapy are emphasized.

Denko, C. W., and Schroeder, L. R.: Ecchymotic skin lesions in patients receiving prednisone. J.A.M.A., 164:41-43 (May 4) 1957.

Purpurae, ecchymotic skin lesions and easy bruising were noted in 20 per cent of a group of seventy-five patients given prednisone for rheumatological disorders.

News Items

FELLOWSHIPS IN RESEARCH AND CLINICAL ALLERGY

The American Foundation for Allergic Diseases announces the establishment of Fellowships in research and clinical allergy for a two-year period, carrying a stipend of $4,500 for the first year and $4,750 for the second with an additional $750 for laboratory and travel expenses during the two-year period.

Candidates must be graduates of approved medical schools and have completed the graduate training preliminary to certification by the Boards of Internal Medicine or Pediatrics.

Application requests may be addressed to: Dr. Colin M. MacLeod, Prof. of Research Medicine, University of Pennsylvania, 820 Maloney Clinic, 36th and Spruce Streets, Philadelphia 4, Pennsylvania; or to Dr. Herman N. Eisen, Prof. of Medicine (Dermatology), Washington University School of Medicine, Saint Louis, Missouri.

Applications should be filed by December 15, 1957. Notifications will be given by February 1, 1958.

ALLERGY SESSION OF THE AMERICAN MEDICAL ASSOCIATION, JUNE, 1958

Co-chairmen of the allergy session of the American Medical Association are Dr. Orval R. Withers and Dr. William B. Sherman. The secretary is Dr. R. Dale Dickson. Physicians wishing to present papers at the meeting in San Francisco in June, 1958, are requested to send abstracts of 250 words in triplicate to the secretary at 1008 Kansas Avenue, Topeka, Kansas. The physicians whose papers are accepted will be notified at the earliest possible date.

INTERNATIONAL ASSOCIATION OF ALLERGOLOGY

Announcement is made of the formation of a Nomenclature Committee of the International Association of Allergology. The members of the Committee are as follows:

Dr. Guido Ruiz Moreno (Chairman), Berutti 2895, Buenos Aires, Argentina
Dr. Joseph Harkavy, 1165 Park Avenue, New York, New York
Dr. Umberto Serafini, Via Guisciardini, Florence, Italy
Dr. H. Stork, Talstrasse 41, Zurich, Switzerland
Dr. J. M. Gutmann, 14 Street of the Prophets, Jerusalem, Israel

Fellows of the International Association of Allergology, nonmember physicians, mycologists, bateriologists, immunologists and those interested in allergy are invited to communicate with members of the Committee. Communications in English should be sent to Dr. Harkavy and those in French or Italian to Dr. Serafini; those in German to Dr. Stork and those in Spanish or Portuguese to Dr. Moreno.

ALLERGISTS INVITED TO CENTER LABORATORIES

Allergists are invited to the new building of the Center Laboratories at 16 Secatoag Avenue, Port Washington, New York. The building, recently constructed, is devoted entirely to research and production of allergens, and the testing and standardizing of equipment of interest to allergists. Facilities for animal research and testing, control productions and standardization are available, as is a consultation service.

BOOK REVIEWS

J.A.M.A. CLINICAL ABSTRACTS OF DIAGNOSIS AND TREATMENT. Selected by I. Phillips Frohman, M.D. 554 pages and index. New York & London: Intercontinental Medical Book Corporation, 1957. Price $5.50.

For the *Journal of the American Medical Association,* Dr. Austin Smith, editor, and his staff of physicians select outstanding articles from the more than 1200 leading periodicals published all over the world. "From these," Dr. I. Phillips Frohman says, "I have selected for this volume those which I considered to pertain most directly to the two most important aspects of Clinical Medicine—Diagnosis and Treatment." In this book of 554 pages, listed under the heading of Allergy, are three abstracts, one dealing with gastrointestinal neonatal sensitivity to cow's milk, a second with the topical use of prednisolone in nasal allergy, a third with food sensitivity as a cause of perennial nasal allergy. Since the latter papers were both printed in the ANNALS OF ALLERGY, our journal is well represented. But the field of allergy deserves better treatment.

Under the heading of Asthma are listed four abstracts concerned with "reproducible psychosomatic," nonallergic management of serious asthma and the use of cortisone in the treatment of children with chronic asthma (the drug is not recommended). There are two abstracts concerned with anaphylactic reaction to penicillin, and one of which the subject is periarteritis nodosa. Thrombocytopenic purpura due to quinidine is mentioned once.

How is it determined that although the digestive and urinary systems are given seventy-five and seventy-three pages of abstracts, the respiratory, the endocrine, the blood and lymphatics and the ear, eye, nose, and throat are each given fifty-seven pages? Poisonings, the skin and the reproductive system successively receive thirty, twenty-eight and twenty-six pages, while infections get sixteen, the nervous system, fifteen and the bones and joints, forty pages.

Are these quantitative criteria of importance for diagnosis and treatment in these fields, or do they represent the preferences of the staff of physicians and of the author?

It would be interesting to compare the relative importance given these successive subjects with the occurrence of the disorders listed in General or Specialty Practice.

FLUID AND ELECTROLYTES IN PRACTICE. Harry Statland, M.D. Second Edition. 229 pages, including bibliography and index. Philadelphia—Montreal: J. B. Lippincott Company, 1957. Price $6.00.

Dr. Statland has written a lucid, comprehensive teaching primer of body fluid and electrolytes. He states in his introduction that the present text is not intended as a "source book" or as a comprehensive treatise on the subject. Nevertheless, representing his teaching notes as presented to undergraduate and postgraduate students at the University of Kansas School of Medicine since 1950, the book more than adequately deals with the basic principles of fluid movements and the major abnormalities of volume, concentration and acid-base balance. The chapter on the "Treatment of the Major Depletions," particularly in its list of solutions available for the treatment for water depletion, salt depletion and mixed depletions, is especially useful.

The applications of the principles of fluid balance in the treatment of heart disease, kidney disease, diabetic acidosis, and the subject of pediatric fluid balance, are extremely well discussed.

The intake, output and variations in stress reactions are particularly important to the physician who uses corticosteroids. The discussion on acid-base balance in metabolic alkalosis, respiratory alkalosis and respiratory acidosis and the diagnosis and differential diagnosis of these states should be familiar to all allergists.

A VISIT TO THE HOSPITAL. Written by Francine Chase, under the supervision of Lester L. Coleman, M.D. 68 pages, with illustrations. New York: Grosset & Dunlap, 1957. Price $1.50.

Every so often we, as physicians, must allay the fears and anxieties of children who must be hospitalized either for studies or treatment, medical or surgical. Few of us are skillful in the psychological principles involved in preparing such children for the emotional traumatic experience of the separation from their parents or for surgical procedures.

Francine Chase, supervised by Dr. Lester L. Coleman, has written a pictured book embodying the most modern psychological principles for the preparation of such children. With pictures by James Bama and an introduction by Dr. Flanders Dunbar, this book will do much to prepare children for what they are to face and negate the resentment and anger they may feel because they were not warned of the possible unpleasantness of their hospital experience.

In his foreword, Dr. Coleman lists ten commandments for those whose children as patients are to undergo surgery. They can well be applied to any child who must be subjected to diagnostic or therapeutic procedures.

THE PRESENTATION OF TECHNICAL INFORMATION. Reginald O. Kapp. 147 pages and index. New York: The Macmillan Company, 1957. Price $1.95.

If instead of, "I come to bury Caesar, not to praise him," Anthony had said, "In this case I have undertaken the journey here for the purpose of the interring of the deceased. From this point of view I do not, however, propose putting anything on record in so far as praise is concerned," no one in Shakespeare's day would have listened to Anthony's speech and no one today would read it.

The author has written a book on what he terms Functional English; that is, English that always says exactly what it means, as, for instance, "The waves were high." He compares it with imaginate language which does not exactly say what it means, as, for example, "The waves were rude." The problems in linguistics, in logic and in the psychology of Functional English are discussed with clarity, as are the problems of the selection of material for a report, a paper or a book.

What goes on in the mind of the reader or listener is analyzed under the heading of metaphors as a storehouse of memory, acts of association, the preconscious process, associative limits, the acts of understanding and of memorizing.

The chapter on "Making It Easy To Understand" is worth the price of the book because it discusses, among other things, "comment words," bridges of reasoning, the discipline of bridge building, subsiding bridges, and the do's and don'ts of figures and graphs.

The book's completeness is shown by one chapter on making things easy to remember and on circumlocution, one on generalizations, a third on qualifications, a fourth on "Words," and an important chapter on "Meaning What You Say."

To know this book is to know how to read more critically and to write more lucidly. The author proves his point in showing that the subject of the presentation of technical information need not be dull but rather lively, easily understood and stimulating.

The reviewer read it three times and plans to read it again.